(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 January 2005 (20.01.2005)

PCT

(10) International Publication Number
WO 2005/005382 A2

(51) International Patent Classification[7]: C07D

(21) International Application Number:
PCT/US2004/021273

(22) International Filing Date: 2 July 2004 (02.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/484,892	2 July 2003 (02.07.2003)	US
60/516,559	30 October 2003 (30.10.2003)	US
60/547,481	24 February 2004 (24.02.2004)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS

(57) Abstract: Compounds, compositions, and methods for treating fungal infection by modulating the activity of the fungal kinesin Kip 1 are disclosed.

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COMPOUNDS, COMPOSITIONS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATONS

[0001] This application claims the benefit of co-pending provisional U.S. Applications Serial No. 60/484,892, filed July 2, 2003, Serial No. 60/547,481, filed February 24, 2004, and Serial No. 60/516,559, filed October 30, 2003, each incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to certain compounds that are selective inhibitors of fungal kinesins, particularly Kip1, and are therefore useful in the treatment of fungal infections.

BACKGROUND OF THE INVENTION

[0003] Pathogenic fungi occur world wide and are major agricultural and health pests. Fungal infections in humans range from superficial and cutaneous to deeply invasive and disseminated.

[0004] In the past 20 years, the incidence of fungal infections has increased dramatically—along with the numbers of potentially invasive species. Indeed, fungal infections, once dismissed as a nuisance, have begun to spread so widely that they are becoming a major concern in hospitals and health departments. Fungal infections occur more frequently in people whose immune systems are compromised or suppressed (e.g., because of organ transplantation, cancer chemotherapy, or the human immunodeficiency virus), who have been treated with broad-spectrum antibacterial agents, or who have been subject to invasive procedures (catheters and prosthetic devices, for example).

[0005] The 1980s and 1990s witnessed a steep rise in *Candida* and *Aspergillus* infections (Musial, CE, Cockerill III, FR, Roberts GD. (1988) Clin

Microb Rev 1(4):349-364; Saral R. (1991) Reviews of Infectious Dis 13:487-492). Similar rises have also been noted in zygomycosis, cryptococcosis, histoplasmosis and fusaria infections.

[0006] The current armamentarium of antifungals has limitations in such areas as efficacy (particularly through the increasing appearance of resistant fungal strains), administration (often requiring intravenous administration), and in their side effect profiles. The need to identify new active agents having novel modes of action for treating fungal infections is ever increasing, in which regard the fungal kinesins represent important new targets. Significantly, although fungi are eukaryotes (like mammalian cells) there is relatively little homology between fungal and mamalian kinesins (e.g., fungal kinesin Kip1 and human kinesin KSP). See, e.g., PCT/US03/35669, filed November 6, 2003 and U.S. Serial Number 60/424,423, each of which is incorporated herein by reference. Thus, by selectively targeting inhibition of fungal kinesins (as opposed to human kinesins) it is believed possible to effectively treat fungal infections while decreasing or even eliminating toxic side effects. The present invention provides such agents and methods for their use.

[0007] All patents and publications mentioned in the specification are indicative of the level of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

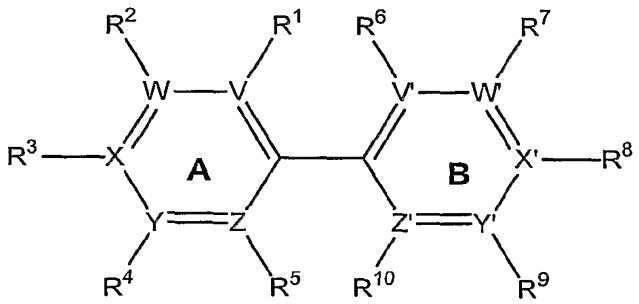
SUMMARY OF THE INVENTION

[0008] In accordance with the objects outlined above, the present invention provides compounds, compositions and methods that can be used to treat fungal infections. The compounds inhibit one or more fungal kinesins.

[0009] In one aspect, the invention relates to methods for a patient having a fungal infection and more particularly, a fungal infection caused by a *Candida* species such as *Candida albicans*, *Candida tropicalis*, *Candida (Torulopsis) glabrata*, *Candida parapsilosis*, *Candida lusitaneae*, *Candida rugosa* and/or *Candida pseudotropicalis*. In certain embodiments, the fungal infection is caused by *Candida albicans*. In certain embodiments, the fungal infection is

caused by a fluconazole resistant strain. Fungal infections which can be inhibited or treated with compositions provided herein include candidiasis including but not limited to onychomycosis, chronic mucocutaneous candidiasis, oral candidiasis, epiglottitis, esophagitis, gastrointestinal infections, genitourinary infections.

[0010] In one aspect, the invention relates to compounds represented by Formula I:



Formula I

wherein:

R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfanyl,

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl;

W, X, Y, Z, W', X', Y' and Z' are independently N, C, O, or S; and

V and V' are independently N, C, O, S or absent

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, provided that:

at least one of R^1, R^2, R^3, R^4 and R^5 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

at least one of V, W, X, Y, Z, V', W', X', Y' and Z' is N, O or S;

no more than two of V, W, X, Y and Z are N;

no more than two of V', W', X', Y' or Z' are N;

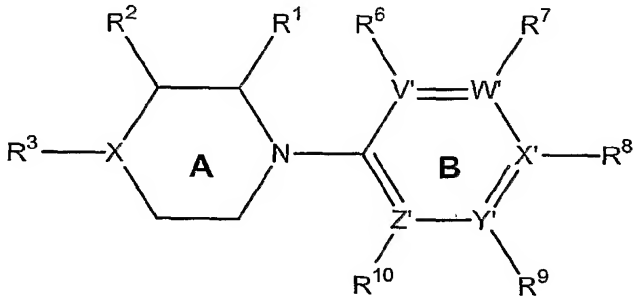
W, X, Y or Z is O or S only when V is absent;

W', X', Y' or Z' is O or S only when V' is absent;

R^1, R^2, R^3, R^4 or R^5 is absent when V, W, X, Y or Z, respectively, is N, O, S or absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent.

[0011] In one aspect, the invention relates to compounds represented by Formula II:



Formula II

wherein:

X is CH or N;

R^1 and R^2 are independently hydrogen, halogen, hydroxyl, or lower alkyl;

R^3 is cyano or sulfonyl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy;

V' is N, C, O, S or absent;

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

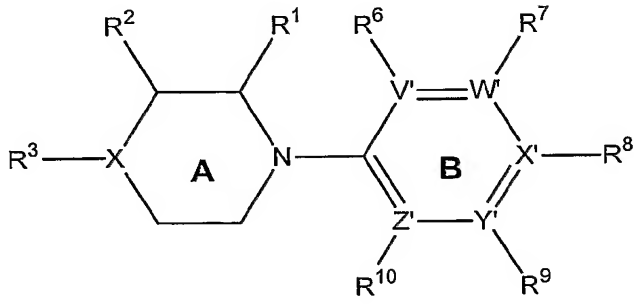
W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N,

O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0012] In one aspect, the invention relates to compounds represented by Formula III:



Formula III

wherein:

X is CH, O or N;

R^1 is hydrogen; and R^2 and R^3 are independently hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl; or R^2 and R^3, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; or

R^1 and R^2, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; and R^3 is hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl;

V' is N, C, O, S or absent,

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0013] In one aspect, the invention relates to compounds represented by Formula IV:

A-B

Formula IV

wherein

A is phenyl, thiophen-3-yl, 1H-pyrrol-3-yl, furan-3-yl, oxazol-4-yl, thiazol-4-yl, or 1H-imidazol-4-yl, each of which is optionally substituted with one or two of the following groups: halogen, optionally substituted phenoxy, optionally substituted benzyl, optionally substituted aminophenyl, lower alkyl, lower alkenyl, trifluoromethyl, difluoromethyl, difluoromethoxy, or trifluoromethoxy; and

B is a 5- or 6-membered heteroaromatic ring which is substituted with one or two of the following groups: optionally substituted amino, acyl, cyano, sulfonyl, nitro, heterocycle, or optionally substituted aminocarbonyl,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0014] The compounds of Formula I, II, III, and IV are useful as active agents in practice of the methods of treatment and in manufacture of the pharmaceutical formulations of the invention, and as intermediates in the synthesis of such active agents.

[0015] In still another aspect, the invention relates to a pharmaceutical formulation comprising a pharmaceutically acceptable excipient, and to a method of treatment for fungal infection, each entailing a therapeutically

effective amount of one or more compounds of Formula I, II, III, and IV and.

[0016] Other aspects and embodiments will be apparent to those skilled in the art form the following detailed description.

DETAILED DESCRIPTION

[0017] The invention will now be described in detail with reference to certain of its embodiments. While the invention is described in conjunction with certain embodiments, it should be understood that such embodiments are not intended as limiting the scope of the invention. The spirit and scope of the invention includes the alternatives, modifications and equivalents to the embodiments specifically set forth in this detailed description.

DEFINITIONS

[0018] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

Abs	=	absent
Bz	=	benzyl
c-	=	cyclo
DMF	=	dimethylformamide
dppf	=	1,1'-bis(diphenylphosphino)ferrocene
eq.	=	equivalent
Et	=	ethyl
EtOAc	=	ethyl acetate
EtOH	=	ethanol
g	=	grams
h	=	hour
Me	=	methyl
min	=	minute
mL	=	milliliter
mmol	=	millimole

nM	=	nanomole
NMP	=	N-methyl-pyrrolidone
Ph	=	phenyl
rt or RT	=	room temperature
s-	=	secondary
t-	=	tertiary
THF	=	tetrahydrofuran

[0019] As used herein the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more.

[0020] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*) that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0021] **Acyl** refers to groups of from 1 to 8 carbon atoms attached to a parent structure through a carbonyl functionality [i.e., -C(O)-]. The carbon atoms can be in a straight, branched or cyclic configuration, whether saturated or unsaturated, aromatic or non-aromatic, and can include combinations thereof. One or more carbons in the acyl residue can be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0022] **Alicyclic** refers to carbocyclic ring structures which may be

saturated or unsaturated, but may not be a benzenoid or other aromatic system.

[0023] **Alkyl** includes linear, branched or cyclic hydrocarbon structures and combinations thereof. **Lower alkyl** refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and the like. Preferred alkyl groups are those of C_{20} or below. More preferred alkyl groups are those of C_{13} or below. Yet more preferred are alkyl groups of C_6 and below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, c-hexyl, norbornyl, adamantyl and the like. In this application, alkyl includes alkanyl, alkenyl and alkynyl residues; it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl and the like. Alkylene is another subset of alkyl, referring to the same residues as alkyl, but having two points of attachment. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$) and cyclohexylpropylene [$-CH_2CH_2CH(C_6H_{13})-$]. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, isobutyl and t-butyl; "propyl" includes n-propyl and isopropyl.

[0024] **Alkenyl** refers to an unsaturated hydrocarbon chain having from 2 to 12 member atoms and having one or more carbon-carbon double bond within the chain. In certain embodiments alkenyl groups have one carbon-carbon double bond within the chain. In other emodiments, alkenyl groups have more than one carbon-carbon double bond within the chain. Alkenyl includes ethylenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0025] **Alkynyl** refers to an unsaturated hydrocarbon chain having from 2 to 12 member atoms and having one or more carbon-carbon triple bond within the chain. In certain embodiments alkynyl groups have one carbon-carbon triple bond within the chain. In other emodiments, alkynyl groups have more than one carbon-carbon triple bond within the chain. For the sake of clarity, unsaturated hydrocarbon chains having one or more carbon-carbon triple bond within the chain and one or more carbon-carbon double bond within the chain are alkynyl groups. Alkynyl includes ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0026] **Amino** refers to the group $-NH_2$.

[0027] **Aryl** and **heteroaryl** mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-4 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-4 (or more) heteroatoms selected from O, N, or S; or a tricyclic 12- to 14-membered aromatic or heteroaromatic ring system containing 0-4 (or more) heteroatoms selected from O, N, or S. The aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0028] **Aralkyl** refers to a residue in which an aryl moiety is attached to the parent structure via an alkylene moiety. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. **Heteroaralkyl** refers to a residue in which a heteroaryl moiety is attached to the parent structure via an alkylene moiety. Examples include furanylmethyl, pyridinylmethyl, pyrimidinylethyl and the like. Aralkyl and heteroaralkyl are included within the scope of substituted alkyl and more specifically, within the scope of substituted methyl.

[0029] ATPase refers to an enzyme that hydrolyzes ATP. ATPases include proteins comprising molecular motors such as the kinesins.

[0030] Optionally substituted **aminocarbonyl** refers to the group $-C(O)NR^bR^c$ where R^b is H or optionally substituted-alkyl, -aryl, -heteroaryl, aralkyl-, or heteroaralkyl, and R^c is H or optionally substituted alkyl. Aminocarbonyl is meant to include carbamoyl, lower-alkyl carbamoyl, benzylcarbamoyl, phenylcarbamoyl, methoxymethylcarbamoyl, and the like.

[0031] **Halogen** or **halo** refers to fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are preferred. Dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0032] **Heterocycle** means a cycloalkyl residue in which one to four of the

carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. The term heterocyclyl encompasses heteroaryl, which is a subset of heterocyclyl. Examples of heterocycles that fall within the scope of the invention include pyrrolidine (and the corresponding unsaturated group, pyrrole), tetrahydroisoquinoline, morpholine, piperidine, dioxane, tetrahydrofuran and the like. **N-Heterocyclyl** refers to a nitrogen-containing heterocycle as a substituent residue. Examples of N-heterocyclyl residues include 4-morpholinyl, 4-thiomorpholinyl, 1-piperidinyl, and 1-pyrrolidinyl. Examples of substituted heterocyclyl include 4-methyl-1-piperazinyl and 4-benzyl-1-piperidinyl.

[0033] **Isolated, purified**, or **biologically pure** refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography.

[0034] **Isomers** are different compounds that have the same molecular formula. **Stereoisomers** are isomers that differ only in the way the atoms are arranged in space. **Enantiomers** are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The symbol "(.±.)" is used to designate a racemic mixture where appropriate. **Diastereoisomers** are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. Absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levo-rotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers can be prepared using chiral synthons or chiral

reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[0035] A **leaving group** or **atom** is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups, except where otherwise specified, are halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[0036] A group name followed by the suffix **-oxy** indicates that the named group is attached to the parent structure via an oxgen atom. **Acyloxy** refers to the group -O-acyl. **Alkoxy** refers to the group –O-alkyl. Similarly, **aryloxy**, **heteroaryloxy**, **aralkoxy** and **heteroaralkoxy** refer to the groups -O-aryl, -O-heteroaryl, -O-aralkyl and –O-heteroaralkyl. **Alkoxycarbonyl** refers to the group –C(O)-O-R^a where R^a is alkyl. **Aryloxycarbonyl** refers to the group –C(O)-O-R^a where R^a is aryl or heteroaryl.

[0037] **Pharmaceutically acceptable carrier** or **pharmaceutically acceptable excipient** includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with an active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0038] **Pharmaceutically acceptable acid addition salt** refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid

and the like.

[0039] **Pharmaceutically acceptable base addition salts** include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine and ethanolamine.

[0040] **Pharmaceutically acceptable esters** refers to esters of compounds of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Examples of pharmaceutically acceptable, non-toxic esters of the present invention include C_1 to C_6 alkyl esters and C_5 to C_7 cycloalkyl esters, although C_1 - to C_4 alkyl esters are preferred. Esters of the compounds of the invention can be prepared according to conventional methods. Pharmaceutically acceptable, non-toxic esters of the present invention also include prodrug ester group, i.e., any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art. Other examples of prodrug ester groups can be found in the book "Pro-drugs as Novel Delivery Systems," by Higuchi and Stella., V. 14 of the A.C.S. Symposium Series.

[0041] **Pharmaceutically acceptable amide** refers to non-toxic amides of the present invention derived from ammonia, primary C_1 to C_6 alkyl amines and secondary C_1 to C_6 dialkyl amines. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1 to C_3 alkyl primary amides and C_1 to C_3 dialkyl secondary amides are preferred. Amides of the compounds of the invention can be prepared according to conventional methods.

[0042] **Subject** or **patient** refers to an animal, preferably a mammal, that has been the object of treatment, observation or experiment, and most preferably refers to a human who has been the object of observation and/or treatment. The methods of the invention are useful in both human therapy and veterinary applications. In some embodiments the patient is a mammal, and in some embodiments the patient is human.

[0043] The term **substituted** as used herein with regard to alkyl, aryl, heteroaryl and heterocyclyl refers respectively to alkyl, aryl, heteroaryl and heterocyclyl groups wherein one or more (up to about 5, preferably up to about 3) hydrogen atoms are replaced by a substituent independently selected from the group: optionally substituted alkyl (e.g., fluoroalkyl such as trifluoromethyl), optionally substituted alkoxy, alkoxycarbonyl [i.e., esters or –C(O)OR], alkylenedioxy (e.g., methylenedioxy), optionally substituted amino (e.g., alkylamino and dialkylamino), optionally substituted amidino, optionally substituted aryl (e.g., phenyl), optionally substituted aralkyl (e.g., benzyl), optionally substituted aryloxy (e.g., phenoxy), optionally substituted aralkoxy (e.g., benzyloxy), carboxy [-C(O)OH], carboalkoxy [i.e., acyloxy or –OC(O)R], carboxamido, aminocarbonyl, benzyloxycarbonylamino (CBZ-amino), cyano, carbonyl, halo, hydroxy, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted heteroaryloxy, optionally substituted heteroaralkoxy, nitro, sulfanyl, sulfinyl, sulfonyl, and thio.

[0044] **Substituted alkoxy** refers to the group -O-(substituted alkyl). One preferred substituted alkoxy group is "polyalkoxy" or -O-(optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of about 2-20, preferably about 2-10, and more preferably about 2-5. Another preferred substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is an integer of about 1-10, preferably about 1-4.

[0045] **Substituted amino** refers to the group -NHR or -NRR where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted amino, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, urea,

acyl, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, e.g., diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino. Substituted amino includes such groups as $-NR^cC(O)R^b$, $-NR^cCO_2R^a$, and $-NR^cC(O)NR^bR^c$, where: R^a is optionally substituted-lower alkyl, -aryl, heteroaryl, aralkyl or heteroaralkyl; R^b is hydrogen, optionally substituted-lower alkyl, -aryl, heteroaryl, aralkyl or heteroaralkyl; and R^c is hydrogen or lower alkyl.

[0046] **Sulfanyl** refers to the groups: -S-alkyl, -S-aryl, -S-heteroaryl and -S-heterocyclyl, in which each of the groups attached to –S- should be understood to encompass optional substitutions.

[0047] **Sulfinyl** refers to the groups: -S(O)-H, -S(O)-alkyl, -S(O)-aryl, -S(O)-heteroaryl), and -S(O)-heterocyclyl, in which each of the groups attached to -S(O)- should be understood to encompass optional substitutions.

[0048] **Sulfonyl** refers to the groups: $-S(O)_2H$, $-S(O)_2$-alkyl, $-S(O)_2-NH_2$, $-S(O)_2$-NH-alkyl, $-S(O)_2$-NH-aryl, $-S(O)_2$-NH-heteroaryl, $-S(O)_2$-aryl, $-S(O)_2$-aralkyl, $-S(O)_2$-heteroaryl, $-S(O)_2$-heteroaralkyl, $-S(O)_2$-heterocyclyl, $-S(O)_2$-alkoxy, $-S(O)_2$-aryloxy, $-S(O)_2$-heteroaryloxy and $-S(O)_2$-heterocyclyloxy, in which each of the groups attached to $-S(O)_2-$ should be understood to encompass optional substitutions.

[0049] **Therapeutically effective amount** means that amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue system, animal or human that is being sought by a research, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

[0050] **Treatment** or **treating** means any treatment of a disease in a mammal, including:

a) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

b) inhibiting the disease, that is, slowing or arresting the development of clinical symptoms; and/or

c) relieving the disease, that is, causing the regression of clinical symptoms.

[0051] It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of

solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention.

[0052] Some of the crystalline forms for the compounds may exist as polymorphs and as such are included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also encompassed within the scope of this invention.

[0053] The present invention includes within its scope prodrugs of the compounds shown herein. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compounds specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to a subject in need thereof. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", H. Bundgaard ed., Elsevier, 1985. Protected forms of the inventive compounds are included within the scope of the present invention.

[0054] Implicit hydrogen atoms are omitted from the formulae for clarity, but should be understood to be present.

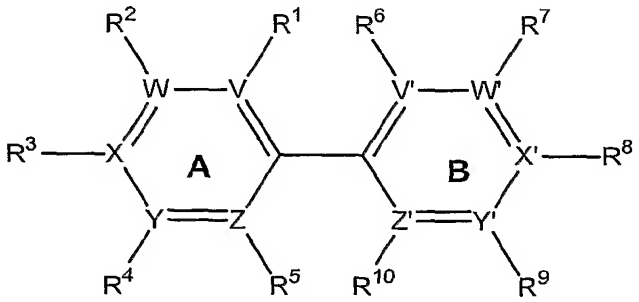
COMPOUNDS OF THE INVENTION

[0055] The p resent invention is directed to a class of novel compounds that are inhibitors of one or more fungal kinesins. In accordance with certain embodiments of the invention, the disclosed compounds inhibit the fungal kinesin *Candida albicans* Kip1. See, also, PCT/US03/35669, filed November 6, 2003 and U.S.S.N. 60/424,423, filed November 6, 2002, incorporated herein by reference for all purposes. In certain embodiments, the compounds inhibit *Candida albicans* Kip1, as well as modulating the activity of one or more of the fungal kinesins selected from the group consisting of *Aspergillus fumigatus* bimC; *C. parapsilosis* Kip1; *C. glabrata* CIN8; *C. glabrata* Kip1; *C. tropicalis*

Kip1; and *C. Krusei* Kip1. In certain embodiments, the compounds inhibit fluconazole resistant strains of *Candida albicans*.

[0056] The methods of inhibiting a fungal kinesin comprise contacting a compound of Formula I, II, III, and IV with a fungal kinesin, more particularly, *C. albicans* Kip1 or fragments and variants thereof.

[0057] In certain embodiments, the invention relates to compound represented by Formula I:



Formula I

wherein:

R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfanyl,

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl;

W, X, Y, Z, W', X', Y' and Z' are independently N, C, O, or S; and

V and V' are independently N, C, O, S or absent

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, provided that:

at least one of R^1, R^2, R^3, R^4 and R^5 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

at least one of V, W, X, Y, Z, V', W', X', Y' and Z' is N, O or S;

no more than two of V, W, X, Y and Z are N;

no more than two of V', W', X', Y' or Z' are N;

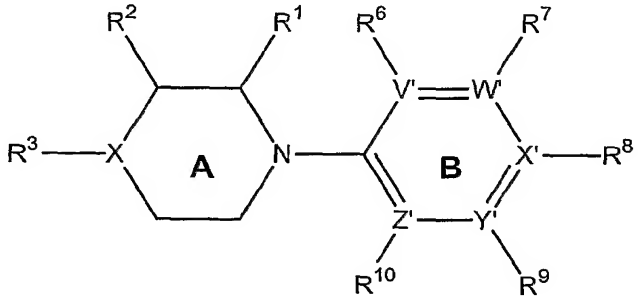
W, X, Y or Z is O or S only when V is absent;

W', X', Y' or Z' is O or S only when V' is absent;

R^1, R^2, R^3, R^4 or R^5 is absent when V, W, X, Y or Z, respectively, is N, O, S or absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent.

[0058] In one aspect, the invention relates to compounds represented by Formula II:



Formula II

wherein:

X is CH or N;

R^1 and R^2 are independently hydrogen, halogen, hydroxyl, or lower alkyl;

R^3 is cyano or sulfonyl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy;

V' is N, C, O, S or absent;

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

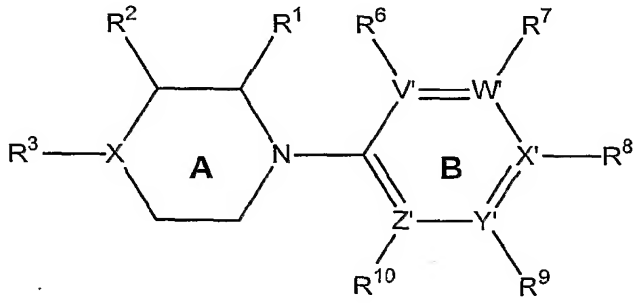
W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N,

O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0059] In one aspect, the invention relates to compounds represented by Formula III:



Formula III

wherein:

X is CH, O or N;

R^1 is hydrogen; and R^2 and R^3 are independently hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl; or R^2 and R^3, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; or

R^1 and R^2, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; and R^3 is hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl;

V' is N, C, O, S or absent,

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0060] In one aspect, the invention relates to compounds represented by Formula IV:

A-B

Formula IV

wherein

A is phenyl, thiophen-3-yl, 1H-pyrrol-3-yl, furan-3-yl, oxazol-4-yl, thiazol-4-yl, or 1H-imidazol-4-yl, each of which is optionally substituted with one or two of the following groups: halogen, optionally substituted phenoxy, optionally substituted benzyl, optionally substituted aminophenyl, lower alkyl, lower alkenyl, trifluoromethyl, difluoromethyl, difluoromethoxy, or trifluoromethoxy; and

B is a 5- or 6-membered heteroaromatic ring which is substituted with one or two of the following groups: optionally substituted amino, acyl, cyano, sulfonyl, nitro, heterocycle, or optionally substituted aminocarbonyl,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0061] The compounds of Formula I, II, III, and IV are useful as active agents in practice of the methods of treatment and in manufacture of the pharmaceutical formulations of the invention, and as intermediates in the synthesis of such active agents.

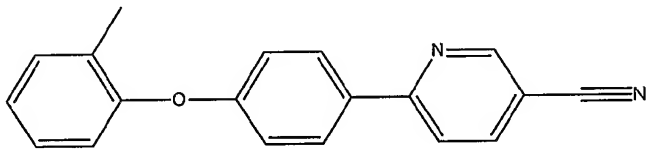
[0062] In still another aspect, the invention relates to a pharmaceutical formulation comprising a pharmaceutically acceptable excipient, and to a method of treatment for fungal infection, each entailing a therapeutically

effective amount of one or more compounds of Formula I, II, III, and IV and. Other aspects and embodiments will be apparent to those skilled in the art form the following detailed description.

[0063] The compounds Formula I, II, III, and IV are useful as active agents in practice of the methods of treatment and in manufacture of the pharmaceutical formulations of the invention, and as intermediates in the synthesis of such active agents.

NOMENCLATURE

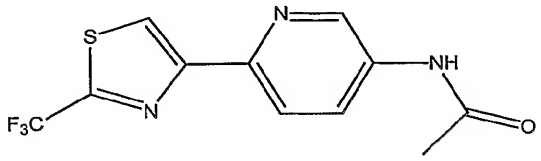
[0064] The compound of Formula IA:



Formula IA

i.e., the compound of Formula I where V, W, X, Y, Z, W', X', Y' and Z' are C, V' is N, R^1, R^2, R^4, R^5, R^6, R^7, R^9 and R^{10} are H, R^3 is 2-methyl-phenoxy and R^8 is cyano, can be named 6-(4-*o*-tolyloxy-phenyl)-nicotinonitrile.

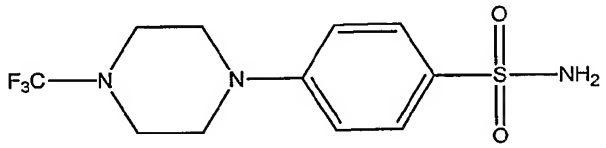
[0065] The compound of Formula IB:



Formula IB

i.e., the compound of Formula I where V, R^1, R^3, R^5 and R^6 are absent, X is S, Z and V' are N, W, Y, W', X', Y' and Z' are C, R^2, R^7, R^9 and R^{10} are H, R^4 is trifluoromethyl and R^8 is acetylamino, can be named *N*-[6-(2-trifluoromethyl-thiazol-4-yl)-pyridin-3-yl]-acetamide.

[0066] The compound of Formula IIA:



Formula IIA

i.e., the compound of Formula III where V, W, Y, Z, V', W', X', Y' and Z' are C, X

is N, R^1, R^2, R^6, R^7, R^9 and R^{10} are H, R^3 is trifluoromethyl and R^8 is aminosulfonyl, can be named 4-(4-trifluoromethyl-piperazin-1-yl)-benzenesulfonamide.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

[0067] The compounds of the invention can be synthesized utilizing techniques well known in the art, e.g., as illustrated below with reference to the Reaction Schemes.

SYNTHETIC REACTION PARAMETERS

[0068] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10°C to 110°C. Further, except as employed in the Examples or as otherwise specified, reaction times and conditions are intended to be approximate. For example, the language "taking place at atmospheric pressure within a temperature range of -10°C to about 110°C over a period of 1 to 24 hours" should be read to mean "taking place at about atmospheric pressure within a temperature range of about -10°C to about 110°C over a period of about 1 to about 24 hours." Reactions typically left to run overnight average a period of about 16 hours.

[0069] The terms "solvent", "organic solvent" or "inert solvent" each mean a solvent inert under the conditions of the reaction described in conjunction therewith [including, for example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents.

[0070] Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the

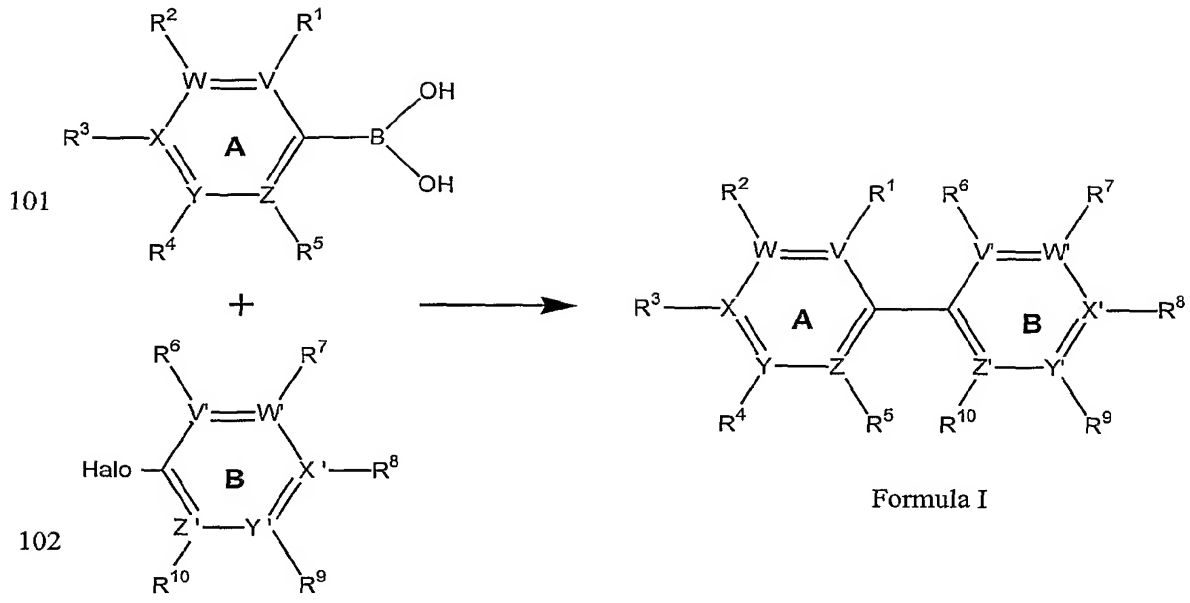
examples hereinbelow. Other equivalent separation or isolation procedures can, of course, also be used.

[0071] Methods for the determination of stereochemistry and the separation of stereoisomers are well known to a person of ordinary skill in the art [see the discussion in Chapter 4 of J. March, "Advanced Organic Chemistry", 4th ed., John Wiley and Sons, New York, N.Y., 1992]. When desired, the (R)- and (S)-isomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. For example, a compound can be dissolved in a lower alkanol and placed on a Chiralpak AD column (Chiral Technologies, Inc.). It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

MATERIALS

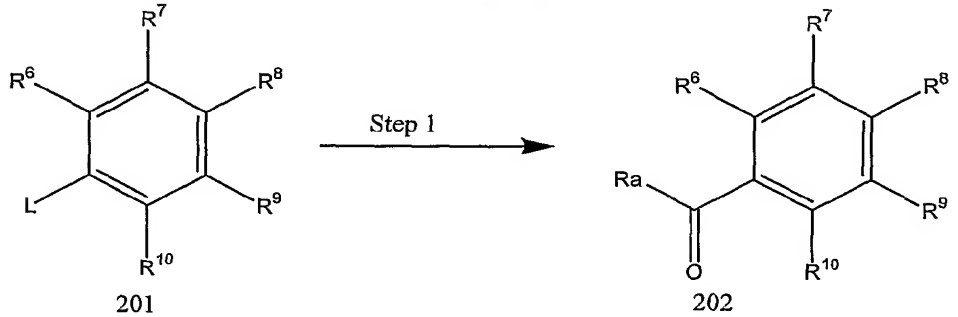
[0072] Many of the optionally substituted starting compounds (e.g., Formulae 101, 102 and 202) and other reactants are commercially available or can be readily prepared by those skilled in the art using commonly employed synthetic methodology starting from substituted benzoic acids that are commercially available (e.g., from Aldrich Chemical Company, Milwaukee, WI).

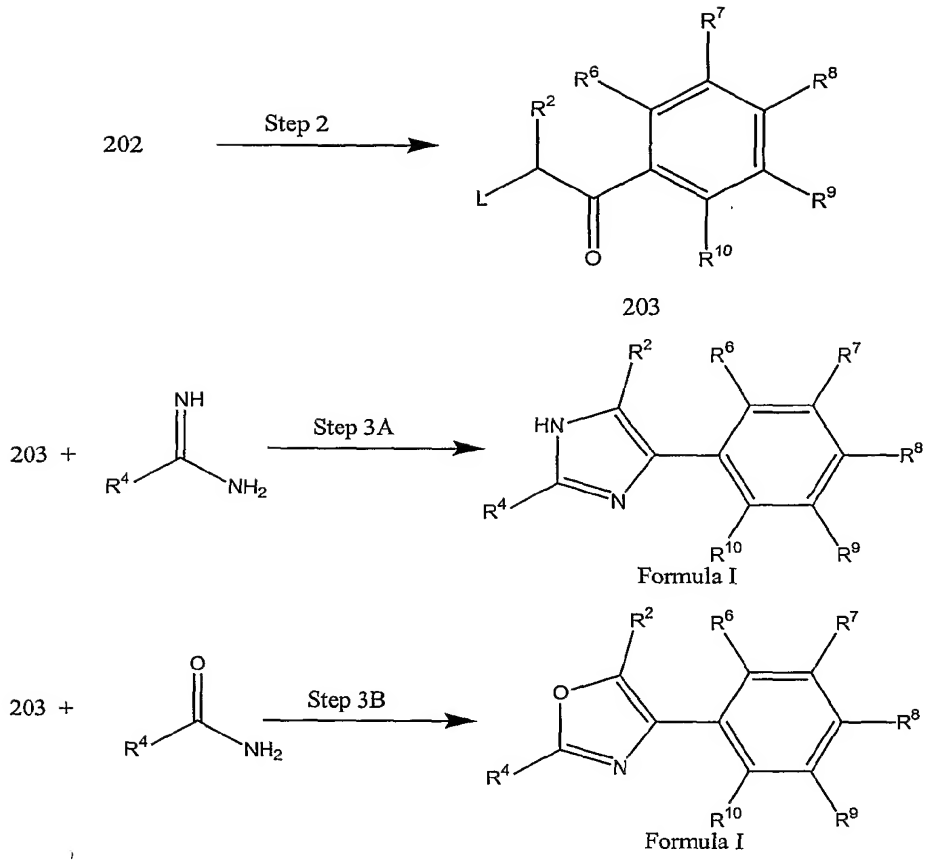
Reaction Scheme 1



[0073] A mixture is made of: a boronic acid of Formula 101 (1.1 equivalents), a halogenated compound of Formula 102 (1 equivalent), a palladium catalyst [such as $Pd(PPh_3)_4$ (0.1 equivalents)], a base such as 2 M aqueous Na_2CO_3 (3 equivalents), and an inert solvent such as toluene (0.2 M to bromide). The mixture is heated to about 100°C for about 12 hours. The reaction mixture is then cooled and the solvent layer is washed (e.g., with saturated aq NaCl), dried (e.g., with $MgSO_4$), and concentrated to afford the corresponding compound of Formula I.

Reaction Scheme 2





Preparation of Formula 202 where R_a is Hydrogen or Methyl

[0074] Referring to Reaction Scheme 2, Step 1, a solution of a compound of Formula 201, wherein L is a leaving group (especially Cl, Br, I, or -OTf); a palladium catalyst such as $Pd(PPh_3)_4$; about an equivalent of n-butyl vinyl ether; a base such as Et_3N, and an aprotic solvent such as DMF, is stirred for about 1-16 hr at about 80°C. The product, a compound of Formula 202 wherein R_a is methyl, is isolated and optionally purified.

[0075] Referring to Reaction Scheme 2, Step 1, a solution of a compound of Formula 201, wherein X is a leaving group (especially Cl, Br, I, or -OTf); a palladium catalyst such as $Pd(PPh_3)_4$; about an equivalent of triethylammonium formate; gaseous carbon monoxide; and an aprotic solvent such as DMF is stirred at about 80°C for about 1-16 hr. The product, a compound of Formula 202, wherein R_a is hydrogen, is isolated and optionally purified.

Preparation of Formula 203

[0076] Referring to Reaction Scheme 2, Step 2, the compounds of Formula 202 wherein R_a is methyl or hydrogen can be readily converted to

compounds of Formula 203 where R_a becomes $-CHLR^2$, wherein L is a leaving group (especially bromo or chloro) and R^2 is optionally substituted alkyl, alkoxycarbonyl, cyano or carboxamido, using techniques known in the art. Alternatively, compounds of Formula 202 wherein R_a is methyl can be treated with a brominating reagent such as tetraethyl-ammonium tribromide or tetramethyl-ammonium tribromide to yield the corresponding compound of Formula 202 wherein R_a is $-CH_2Br$.

Compounds of Formula I

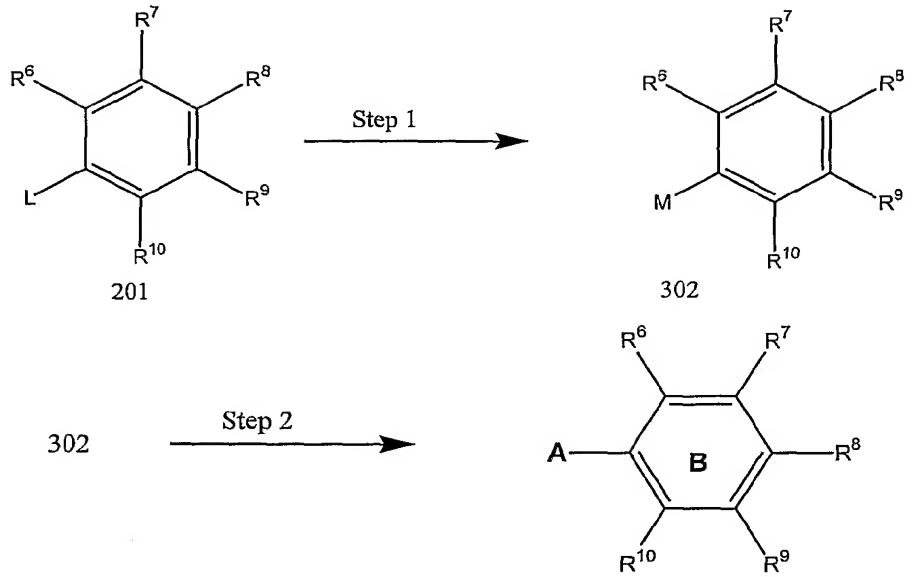
[0077] Referring to Reaction Scheme 2, Step 3A, compounds of Formula I where Ring A is optionally substituted imidazolyl- can be prepared by heating a compound of Formula 203 [where L is a leaving group (especially bromo or chloro) and R^2 is optionally substituted alkyl, alkoxycarbonyl, cyano, or carboxamido] in a polar, protic solvent such as ethanol with multiple equivalents of a compound of the formula $NH_2C(NH)R^4$ wherein R^4 is $-NH_2$, -NHAc, $-CH_2CN$, -CN, -alkyl, alkoxycarbonyl, or carboxamido.

[0078] Referring to Reaction Scheme 2, Step 3B, compounds of Formula I, wherein Ring A is optionally substituted oxazolyl can be prepared by heating a compound of Formula 203 [where L is a leaving group (especially bromo or chloro) and R^2 is optionally substituted alkyl, alkoxycarbonyl, cyano, or carboxamido] in a polar, protic solvent such as ethanol with multiple equivalents of a compound of the formula $NH_2C(O)R^4$ wherein R^4 is $-NH_2$, -NHAc, $-CH_2CN$, -CN, -alkyl, alkoxycarbonyl, or carboxamido.

[0079] Similarly, compounds of Formula I, wherein Ring A is optionally substituted thiazolyl can be prepared by heating a compound of Formula 203 [where L is a leaving group (especially bromo or chloro) and R^2 is optionally substituted alkyl, alkoxycarbonyl, cyano, or carboxamido] in a polar, protic solvent such as ethanol with multiple equivalents of a compound of the formula $NH_2C(S)R^4$ wherein R^4 is $-NH_2$, -NHAc, $-CH_2CN$, -CN, -alkyl, alkoxycarbonyl, or carboxamido.

[0080] Similarly, compounds of Formula I, wherein Ring A is optionally substituted pyrrazolyl can be prepared by condensing a compound of Formula 202, wherein R_a is -CClCHCN with H_2NNHR^2 in water wherein R^2 is H, alkyl, alkoxycarbonyl, or carboxamido.

Reaction Scheme 3



Formula 2

Preparation of Compounds of Formula 302

[0081] Referring to Reaction Scheme 3, Step 1, the organometallic species of formula 302, wherein M is $B(OH)_2$, ZnX, or trialkyltin, can be either purchased or prepared from precursors 201 using procedures familiar to those in the art.

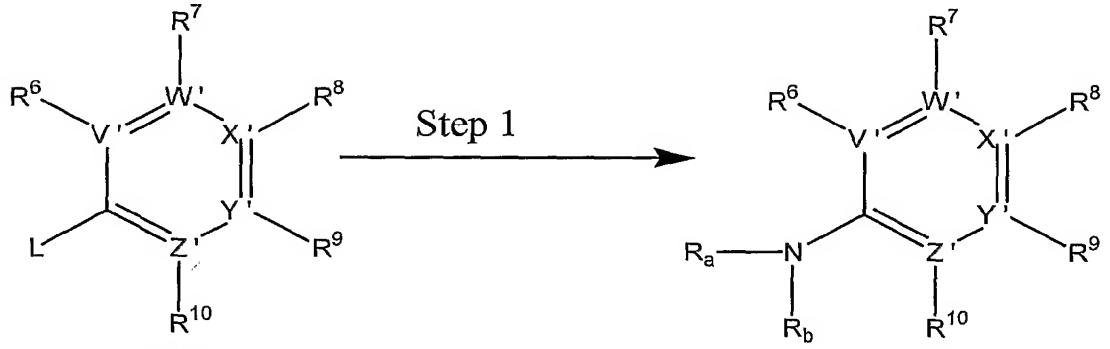
Preparation of Compounds of Formula I

[0082] Referring to Reaction Scheme 3, Step 2, a compound of Formula 302 is treated with a compound of the formula Ring A-L wherein L is a leaving group (especially Cl, Br, I, or $-OSO_2CF_3$), using Pd catalyzed cross coupling procedures as familiar to those in the art. The product, a compound of Formula I, is isolated and optionally purified.

[0083] Alternatively, referring to Reaction Scheme 3, Step 2, a solution of a compound of Formula 302, wherein L is a leaving group (especially Cl, Br, I, or -OTf), a palladium catalyst such as $Pd(Cl)_2(dppf)$; about an equivalent of pinacolato-boronic ester; a base such as KOAc, and an aprotic solvent such as DMF, are heated at about 60-125°C for 10 min to 2 hour. To this reaction mixture is added Ring A-L wherein L is a leaving group (especially Cl, Br, I, or $-OSO_2CF_3$) and a base such as aq. $NaHCO_3$ and heating continued at about 60-

125°C for 1 to 16 hours. The product, a compound of Formula I, is isolated and optionally purified.

Reaction Scheme 4



401 **402**

[0084] Referring to Reaction Scheme 4, a compound of Formula 401 where L is a leaving group (especially F, Cl, Br, I, or –OTf) and a primary or secondary amine of the formula HNR_aR_b (where NR_aR_b corresponds to Ring B of Formula II or a precursor thereto) are dissolved in an aprotic solvent such as THF, DMF or NMP, and condensed at about 0-125°C for about 1 to 48 hours. The product, a compound of Formula 402 (which can be an end product of Formula II or a precursor thereto depending upon choice of primary or secondary amine) is isolated and optionally purified. Precursor compounds of Formula 402 can be cyclized to give the corresponding compound of Formula I, II, III, or IV using procedures familiar to those in the art.

Processes and Last Steps

[0085] A compound of Formula I, II, III, or IV is contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salt.

[0086] A pharmaceutically acceptable acid addition salt of Formula I, II, III, or IV is contacted with a base to form the corresponding free base of Formula I, II, III, or IV.

Representative Compounds

[0087] When considering the compounds of Formula I, in certain

embodiments, R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl.

[0088] In certain embodiments of compounds of Formula I, R^1 is hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl. In certain embodiments, V is absent; X is S; W, Y, and Z are C; and R^1 is absent. In certain embodiments, V is C and R^1 is hydrogen or halogen. In certain embodiments, R^1 is fluoro.

[0089] In certain embodiments of compounds of Formula I, R^2 is hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl. In certain embodiments, R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl. In certain embodiments, R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl. In certain embodiments, R^2 is hydrogen.

[0090] In certain embodiments of compounds of Formula I, R^3 is hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl. In certain embodiments, X is S and R^3 is absent. In certain embodiments, R^3 is hydrogen, halogen, optionally substituted phenoxy, lower alkyl, lower alkenyl, trifluoromethyl, or trifluoromethoxy. In certain embodiments, R^3 is fluoro, chloro, phenoxy, 2-methylphenoxy-, 3-methylphenoxy-, 3-chlorophenoxy, 4-hydroxyphenoxy-, 2-chlorophenoxy-, 4-fluorophenoxy, 3-fluorophenoxy, 2-fluorophenoxy, 3-methoxyphenoxy-, 3-trifluoromethylphenoxy-, 2-fluoro-4-chlorophenoxy-, trifluoromethoxy, trifluoromethyl, propyl, methyl, or propenyl.

[0091] In certain embodiments, one of R^2 or R^3 is trifluoromethyl, trifluoromethoxy, or isopropyl; and the other is hydrogen or fluoro.

[0092] In certain embodiments of compounds of Formula I, R^4 is hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl,

optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl. In certain embodiments, R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl. In certain embodiments, R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl.

[0093] In certain embodiments, R^2 is hydrogen and R^4 is trifluoromethyl, trifluoromethoxy, propenyl, styrenyl, 1-methylbenzyl-, 4-chlorobenzyl, 4-chlorobenzyl, 2-chloro-4-fluorobenzyl, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-methoxybenzyl, bromo, cyclopropyl, t-butyl, or isopropyl.

[0094] In certain embodiments of compounds of Formula I, R^5 is hydrogen, halo, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfonyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, Z is N and R^5 is absent.

[0095] In certain embodiments of compounds of Formula I, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl.

[0096] In certain embodiments of compounds of Formula I, R^6 is hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl. In certain embodiments, V' is N and R^6 is absent. In certain embodiments, V' is C and R^6 is hydrogen.

[0097] In certain embodiments of compounds of Formula I, R^7 is hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl. In certain embodiments, R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl. In certain embodiments, R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-. In certain embodiments, R^7 is hydrogen.

[0098] In certain embodiments of compounds of Formula I, R^8 is hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl. In certain embodiments, R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl. In certain embodiments, R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino-. In certain embodiments, R^8 is cyano or cyanoamino-.

[0099] In certain embodiments of compounds of Formula I, R^9 is hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl. In certain embodiments, R^9 is hydrogen.

[00100] In certain embodiments of compounds of Formula I, R^{10} is hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl. In certain embodiments, R^{10} is hydrogen.

[00101] In certain embodiments of compounds of Formula I,

V is absent, X is S, and W, Y, and Z are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

[00102] In some embodiments,

V is absent, X is S, and W, Y, and Z are C;

R^1 is absent;

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl;

R^3 is absent;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl (especially, trifluoromethyl, trifluoromethoxy, propenyl, styrenyl, 1-methylbenzyl-, 4-chlorobenzyl, 4-chlorobenzyl, 2-chloro-4-fluorobenzyl, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-methoxybenzyl, bromo, cyclopropyl, t-butyl, or isopropyl);

R^5 is hydrogen;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-; and

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino- (especially, cyano or cyanoamino);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00103] In certain embodiments of compounds of Formula I,

V is absent, X is S, Z is N, and W and Y are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is absent;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

[00104] In certain embodiments,

V is absent, X is S, Z is N, and W and Y are C;

R^1 is absent;

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl (especially, hydrogen);

R^3 is absent;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl (especially, R^4 is trifluoromethyl, trifluoromethoxy, propenyl, styrenyl, 1-methylbenzyl-, 4-chlorobenzyl, 4-chlorobenzyl, 2-chloro-4-fluorobenzyl, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-methoxybenzyl, bromo, cyclopropyl, t-butyl, or isopropyl);

R^5 is absent;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-;

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino- (especially, cyano or cyanoamino);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00105] In certain embodiments of compounds of Formula I,

V, W, X, Y, and Z are C;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is hydrogen, halogen, optionally substituted phenoxy, lower alkyl, lower alkenyl, trifluoromethyl, or trifluoromethoxy;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

[00106] In certain embodiments of compounds of Formula I,

V, W, X, Y, and Z are C;

R^1 is fluoro;

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl;

R^3 is fluoro, chloro, phenoxy, 2-methylphenoxy-, 3-methylphenoxy-, 3-chlorophenoxy, 4-hydroxyphenoxy-, 2-chlorophenoxy-, 4-fluorophenoxy, 3-fluorophenoxy, 2-fluorophenoxy, 3-methoxyphenoxy-, 3-trifluoromethylphenoxy-, 2-fluoro-4-chlorophenoxy-, trifluoromethoxy, trifluoromethyl, propyl, methyl, or propenyl;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl;

R^5 is hydrogen;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-;

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino- (especially, cyano or cyanoamino-);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00107] In certain embodiments, ring B is nicotinonitrile-6-yl and ring A is:

4-fluoro-3-trifluoromethyl-phenyl,
2-methylphenoxy,
3-chloro-4-trifluoromethoxy-phenyl,
5-benzyl-thiazol-3-yl,
5-benzyl-thien-2-yl,
biphen-3-yl
2-bromothien-4-yl,
5-(4-chlorobenzyl)-thien-2-yl,
4-chloro-5-isopropenylphenyl,
5-(4-chlorobenzyl)-thiazol-2-yl,
5-(2-chloro-4-fluorobenzyl)-thiazol-2-yl,
4-chloro-5-methylphenyl,
2-chlorophenoxyphenyl,
3-chlorophenoxyphenyl,
3-chlorophenyl,
4-chloro-5-fluorophenyl,
4-chloro-3-trifluoromethylphenyl,
4-cyano-5-trifluoromethylphenyl,
3-cyclohexylphenyl,
3-cyclopropylphenyl,
5-cyclopropyl-thiazol-2-yl,
2-(2,4-dichlorobenzyl)-thiazol-4-yl,
3-difluoromethoxyphenyl,

3-(1,1-difluoropropyl)phenyl,
3-ethylphenyl,
2-(2-fluorobenzyl)-thiazol-4-yl,
2-(3-fluorobenzyl)-thiazol-4-yl,
2-(4-fluorobenzyl)-thiazol-4-yl,
4-(3-fluorophenoxy)-phenyl,
4-(4-fluorophenoxy)-phenyl,
4-fluoro-3-isopropenylphenyl,
2-fluorophenoxyphenyl,
2-fluoro-3-trifluoromethylphenyl,
2-fluoro-3-trifluoromethylphenyl,
3-fluoro-4-trifluoromethylphenyl,
4-(4-hydroxyphenoxy)-phenyl,
5-isopropenyl-thiazol-2-yl,
5-isopropyl-thiazol-2-yl,
3-isopropyl-phenyl,
2-isopropenyl-thien-4-yl,
2-isopropyl-thien-4-yl,
2-isopropyl-thien-5-yl,
3-isopropyl-4-fluorophenyl,
5-(1-Phenyl-ethyl)-thiophen-3-yl,
2-(4-Chloro-2-fluoro-benzyl)-thiazol-4-yl,
2-tert-Butyl-thiazol-4-yl,
5-tert-Butyl-thiophen-3-yl,
5-Isopropyl-thiophen-3-yl,
2-(3-methoxybenzyl)-thiazol-4-yl,
2-(4-methoxybenzyl)-thiazol-4-yl,
4-(3-methoxyphenoxy)-phenyl,
2-(3-methylbenzyl)-thiazol-4-yl,
5-(4-methylbenzyl)-thiazol-2-yl,
4-(2-methylphenoxy)phenyl,
methyl-phenyl-thiazol-2-yl-amine,
2-(1-methyl-2-phenethyl)-thien-4-yl,

2-(1-methyl-2-phenylvinyl)-thien-4-yl,
3-methylsulfanylphenyl,
4-methyl-5-trifluoromethylphenyl,
4-phenoxyphenyl,
2-(1-phenylvinyl)-thien-4-yl,
2-trifluoromethoxyphenyl,
3-trifluoromethoxyphenyl,
4-trifluoromethoxyphenyl,
4-(3-trifluoromethylphenoxy)-phenyl,
2-trifluoromethyl-benzoic acid methyl ester,
2-trifluoromethyl-thien-4-yl,
3-trifluoromethylphenyl,
3-(2,2,2-trifluoroethyl)phenyl,
2-[1-(4-Chloro-phenyl)-1-methyl-ethyl]-thiazol-4-yl, or
5-trifluoromethyl-thiazol-2-yl.

[00108] In certain embodiments, ring B is pyrimidine-5-carbonitrile and ring A is:

5-benzyl-thiazol-3-yl,
5-tert-Butyl-thiophen-3-yl,
5-benzyl-thien-2-yl,
biphen-3-yl,
2-bromothien-4-yl,
5-(4-chlorobenzyl)-thien-2-yl,
4-chloro-5-isopropenylphenyl,
5-(4-chlorobenzyl)-thiazol-2-yl,
5-(2-chloro-4-fluorobenzyl)-thiazol-2-yl,
4-chloro-5-methylphenyl,
2-chlorophenoxyphenyl,
3-chlorophenoxyphenyl,
3-chlorophenyl,
4-chloro-5-fluorophenyl,
4-chloro-5-trifluoromethylphenyl,

4-cyano-5-trifluoromethylphenyl,
3-cyclohexylphenyl,
3-cyclopropylphenyl,
5-cyclopropyl-thiazol-2-yl,
2-(2,4-dichlorobenzyl)-thiazol-4-yl,
3-difluoromethoxyphenyl,
3-(1,1-difluoropropyl)phenyl,
3-ethylphenyl,
2-(2-fluorobenzyl)-thiazol-4-yl,
2-(3-fluorobenzyl)-thiazol-4-yl,
2-(4-fluorobenzyl)-thiazol-4-yl,
4-(3-fluorophenoxy)-phenyl,
4-(4-fluorophenoxy)-phenyl,
4-fluoro-5-isopropenylphenyl,
2-fluorophenoxyphenyl,
2-fluoro-3-trifluoromethylphenyl,
2-fluoro-3-trifluoromethylphenyl,
3-fluoro-4-trifluoromethylphenyl,
4-(4-hydroxyphenoxy)-phenyl,
5-isopropenyl-thiazol-2-yl,
5-isopropyl-thiazol-2-yl,
2-isopropenyl-thien-4-yl,
2-isopropyl-thien-4-yl,
2-(3-methoxybenzyl)-thiazol-4-yl,
2-(4-methoxybenzyl)-thiazol-4-yl,
4-(3-methoxyphenoxy)-phenyl,
2-(3-methylbenzyl)-thiazol-4-yl,
5-(4-methylbenzyl)-thiazol-2-yl,
4-(2-methylphenoxy)phenyl,
methyl-phenyl-thiazol-2-yl-amine,
2-(1-methyl-2-phenethyl)-thien-4-yl,
2-(1-methyl-2-phenylvinyl)-thien-4-yl,
3-methylsulfanylphenyl,

4-methyl-5-trifluoromethylphenyl,
4-phenoxyphenyl,
2-(1-phenylvinyl)-thien-4-yl,
2-trifluoromethoxyphenyl,
4-trifluoromethoxyphenyl,
4-(3-trifluoromethylphenoxy)-phenyl,
2-trifluoromethyl-benzoic acid methyl ester,
2-trifluoromethyl-thien-4-yl,
3-trifluoromethylphenyl,
2-(2,2,2-trifluoroethyl)phenyl,
5-tert-Butyl-thiophen-3-yl, or
5-trifluoromethyl-thiazol-2-yl.

[00109] In certain embodiments, the compound is :

4-(3-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(3-Isopropyl-phenyl)-oxazol-2-ylamine;
4-(4-Trifluoromethyl-phenyl)-1H-imidazol-2-ylamine;
4-(2-Fluoro-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(2-Chloro-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
2-(2-Amino-oxazol-4-yl)-6-trifluoromethyl-phenol;
4-(2-Methoxy-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(4-Fluoro-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(4-Chloro-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(2-Amino-oxazol-4-yl)-2-trifluoromethyl-benzonitrile;
4-(3-Fluoro-5-trifluoromethyl-phenyl)-oxazol-2-ylamine;
4-(3-Chloro-5-trifluoromethyl-phenyl)-oxazol-2-ylamine;
3-(2-Amino-oxazol-4-yl)-5-trifluoromethyl-phenol;
3-(2-Amino-oxazol-4-yl)-N-methyl-5-trifluoromethyl-benzamide;
4-(2-Fluoro-5-trifluoromethyl-phenyl)-oxazol-2-ylamine;
2-(2-Amino-oxazol-4-yl)-4-trifluoromethyl-phenol;
1-(4-Trifluoromethyl-phenyl)-1H-imidazole;
5-Methyl-4-(4-trifluoromethyl-phenyl)-1H-imidazole;
N-[4-(4-Trifluoromethyl-phenyl)-1H-imidazol-2-yl]-acetamide;
4-(4-Trifluoromethyl-phenyl)-1H-imidazol-2-ylamine;

3-(4-Trifluoromethyl-phenyl)-1H-pyrazole;
5-(4-Trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine;
4-(4-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
5-(4-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
5-(4-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(4-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
5-(4-Trifluoromethyl-phenyl)-pyridin-2-ylamine;
6-(4-Trifluoromethyl-phenyl)-pyridin-2-ylamine;
5-(4-Trifluoromethyl-phenyl)-[1,2,4]thiadiazole;
4-(4-Trifluoromethyl-phenyl)-[1,2,3]thiadiazol-5-ylamine;
1-(4-Trifluoromethyl-phenyl)-piperazine;
4-(3-Trifluoromethyl-phenyl)-1H-imidazol-2-ylamine;
5-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(3-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
5-(3-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
5-(3-Trifluoromethyl-phenyl)-oxazole;
5-(3-Trifluoromethyl-phenyl)-2H-pyrazol-3-ylamine;
5-(3-Trifluoromethyl-phenyl)-pyridin-2-ylamine;
5-Nitro-2-(3-trifluoromethyl-phenyl)-pyridine;
6-(3-Trifluoromethyl-phenyl)-pyridin-2-ylamine;
4-(3,4-Dichloro-phenyl)-thiazol-2-ylamine;
4-(4-Phenoxy-phenyl)-thiazol-2-ylamine;
[4-(4-Phenoxy-phenyl)-thiazol-2-yl]-acetonitrile;
4-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(2,6-Dichloro-4-trifluoromethyl-phenyl)-thiazol-2-ylamine;
5-[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-isoxazole;
4-(4-tert-Butyl-phenyl)-thiazol-2-ylamine;
3-(4-Trifluoromethyl-phenyl)-1H-pyrazole;
[4-(4-Trifluoromethyl-phenyl)-thiazol-2-yl]-acetonitrile;
4-Trifluoromethyl-5-(3-trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(3-Trifluoromethoxy-phenyl)-thiazol-2-ylamine;

3-(2-Amino-oxazol-4-yl)-5-trifluoromethyl-benzoic acid ethyl ester;
4-(2-Methyl-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
2-Amino-4-(3-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid;
6-(3-Trifluoromethyl-phenyl)-nicotinic acid methyl ester;
6-(3-Trifluoromethyl-phenyl)-pyridin-3-ylamine;
N-[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-acetamide;
2-(3-Methoxy-phenyl)-5-nitro-pyridine;
3-(5-Nitro-pyridin-2-yl)-benzonitrile;
2-(3-Chloro-phenyl)-5-nitro-pyridine;
5-Nitro-2-m-tolyl-pyridine;
5-Nitro-2-(3-nitro-phenyl)-pyridine;
5-Nitro-2-(3-trifluoromethoxy-phenyl)-pyridine;
6-(4-Trifluoromethyl-phenyl)-pyridine-3-sulfonic acid amide;
6-(3-Trifluoromethyl-phenyl)-nicotinonitrile;
N-Methyl-6-(3-trifluoromethyl-phenyl)-nicotinamide; and
6-(3-Trifluoromethyl-phenyl)-nicotinamide.
5-Chloro-2-(3-trifluoromethyl-phenyl)-pyridine;
5-Fluoro-2-(3-trifluoromethyl-phenyl)-pyridine;
N-[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-propionamide;
[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-urea;
1-Methyl-3-[6-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-urea;
1,1-Dimethyl-3-[6-(3-trifluoromethyl-phenyl)-pyridin-3-yl]-urea;
[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-carbamic acid methyl ester;
N-(2-Amino-ethyl)-6-(3-trifluoromethyl-phenyl)-nicotinamide;
[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-methanol;
1-[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-ethanone;
4-(4-Trifluoromethyl-pyridin-2-yl)-benzonitrile;
N-[6-(3-Trifluoromethyl-phenyl)-pyridin-3-yl]-formamide;
4-(6-Trifluoromethyl-pyridin-2-yl)-benzonitrile;
6-(3-Trifluoromethyl-phenyl)-pyridin-3-ol;
5-(3-Trifluoromethyl-phenyl)-pyridine-2-carbonitrile;
5-(4-Trifluoromethyl-phenyl)-pyridine-2-carbonitrile;
5-Methanesulfonyl-2-(4-trifluoromethyl-phenyl)-pyridine;

5-(4-Trifluoromethyl-phenyl)-1H-pyridin-2-one;

[6-(4-Trifluoromethyl-phenyl)-pyridin-3-yl]-acetonitrile;

5-(4-Trifluoromethyl-phenyl)-pyrimidine-2-carbonitrile;

6-(3-Fluoro-4-trifluoromethyl-phenyl)-nicotinonitrile;

1-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-ethanone;

4-(4-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid methyl ester;

4-(4-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Trifluoromethyl-phenyl)-piperidine-1-carbonitrile;

1-(4-Trifluoromethyl-phenyl)-piperidine-4-carbonitrile;

4-(4-Trifluoromethyl-phenyl)-piperazine-1-sulfonic acid amide;

1-(4-Trifluoromethyl-phenyl)-piperidine-4-carboxylic acid amide;

1-(2-Chloro-4-trifluoromethyl-phenyl)-piperidine-4-sulfonic acid amide;

2-Methyl-4-(3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Fluoro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

1-(4-Fluoro-3-trifluoromethyl-phenyl)-piperidine-4-carbonitrile;

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carboxylic acid methylamide;

4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carbonitrile;

4-(3-Trifluoromethyl-phenyl)-piperidine-1-carbonitrile;

4-(3-Trifluoromethyl-phenyl)-piperidine;

4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid methyl ester;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid methylamide;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid dimethylamide;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carboxylic acid methyl ester;

2-Amino-N-[6-(3-trifluoromethyl-phenyl)-pyridin-3-ylmethyl]-acetamide;

5-(3-Trifluoromethyl-phenyl)-1H-pyridin-2-one;

2-(3-Isopropyl-phenyl)-pyrimidine-5-carbonitrile;

2-m-Tolyl-pyrimidine-5-carbonitrile;

2-(4-Trifluoromethyl-phenyl)-pyrimidine-5-sulfonic acid amide;

5-(3-Trifluoromethyl-phenyl)-pyrazine-2-carbonitrile;

6-(3-Trifluoromethyl-phenyl)-pyridazine-3-carbonitrile;

5-(3-Trifluoromethyl-phenyl)-pyrimidine-2-carbonitrile;
6-(3-Fluoro-5-trifluoromethyl-phenyl)-nicotinonitrile;
4-(5-Trifluoromethyl-pyridin-2-yl)-benzonitrile;
4-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
4-(3-Trifluoromethyl-phenyl)-oxazol-2-ylamine;
5-(3-Trifluoromethyl-phenyl)-thiazol-2-ylamine;
5-(4-Trifluoromethyl-phenyl)-pyridin-2-ylamine;
4-(4-Chloro-3-trifluoromethyl-phenyl)-oxazol-2-ylamine;
N-[6-(4-Trifluoromethyl-phenyl)-pyridin-3-yl]-formamide;
5-(4-Trifluoromethyl-phenyl)-1H-pyridin-2-one;
N-[5-(4-Trifluoromethyl-phenyl)-pyridin-2-yl]-aminosulfonamide;
5-(4-Trifluoromethyl-phenyl)-thiophene-2-sulfonic acid amide;
5-(4-Trifluoromethyl-3-fluoro-phenyl)-thiophene-2-sulfonic acid amide;
4-(5-Isopropyl-thiophen-2-yl)-benzenesulfonamide;
4-(5-Isopropyl-thiophen-3-yl)-benzenesulfonamide;
5-(3-Fluoro-4-trifluoromethyl-phenyl)-thiophen-2-ylamine;
N-[6-(4-Trifluoromethyl-phenyl)-pyridin-3-yl]-aminosulfonamide;
5-(4-Trifluoromethyl-phenyl)-pyridine-2-sulfonic acid amide;
4-(2-tert-Butyl-thiazol-4-yl)-benzonitrile; or
4-[2-(4-Chloro-benzyl)-thiazol-4-yl]-benzonitrile.

[00110] When referring to compounds of Formula II, in certain embodiments, R^1 and R^2 are independently hydrogen, halogen, hydroxyl, or lower alkyl. In certain embodiments, R^1 and R^2 hydrogen.

[00111] When referring to compounds of Formula II, in certain embodiments, R^3 is cyano or sulfonyl. In certain embodiments, R^3 is cyano. In certain embodiments, R^3 is aminosulfonyl-.

[00112] When referring to compounds of Formula II, in certain embodiments, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy.

[00113] In certain embodiments, R^6 is hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl,

optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy. In certain embodiments, R^6 is absent. In certain embodiments, R^6 is hydrogen.

[00114] In certain embodiments, R^7 is hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy. In certain embodiments, R^7 is hydrogen or optionally substituted lower alkyl. In certain embodiments, R^7 is trifluoromethyl.

[00115] In certain embodiments, R^8 is hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy. In certain embodiments, R^8 is hydrogen, halogen, optionally substituted lower alkyl. In certain embodiments, R^8 is fluoro, chloro, methyl, or trifluoromethyl.

[00116] In certain embodiments, R^9 is hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy. In certain embodiments, R^9 is hydrogen.

[00117] In certain embodiments, R^{10} is hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy. In certain embodiments, R^{10} is hydrogen.

[00118] In certain embodiments,

V' is N and W', X' Y', and Z" are C;

X is N;

R^1 and R^2 are hydrogen

R^3 is cyano or sulfonyl;

R^6 is absent;

R^7 is hydrogen or optionally substituted lower alkyl (especially, trifluoromethyl);

R^8 is hydrogen, halogen, optionally substituted lower alkyl (especially, fluoro, chloro, methyl, or trifluoromethyl);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00119] In certain embodiments,

V', W', X' Y', and Z are C;

X is N;

R^1 and R^2 are hydrogen;

R^3 is cyano or sulfonyl;

R^6 is hydrogen;

R^7 is hydrogen or optionally substituted lower alkyl (especially, trifluoromethyl);

R^8 is hydrogen, halogen, optionally substituted lower alkyl (especially, fluoro, chloro, methyl, or trifluoromethyl);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00120] In certain embodiments,

V' is N and W', X' Y', and Z are C;

X is C;

R^1 and R^2 are hydrogen;

R^3 is cyano or sulfonyl;

R^6 is absent;

R^7 is hydrogen or optionally substituted lower alkyl (especially, trifluoromethyl);

R^8 is hydrogen, halogen, optionally substituted lower alkyl (especially, fluoro, chloro, methyl, or trifluoromethyl);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00121] In certain embodiments,

V', W', X' Y', and Z are C;

X is C;

R^1 and R^2 are hydrogen;

R^3 is cyano or sulfonyl;

R^6 is hydrogen;

R^7 is hydrogen or optionally substituted lower alkyl (especially, trifluoromethyl);

R^8 is hydrogen, halogen, optionally substituted lower alkyl (especially, fluoro, chloro, methyl, or trifluoromethyl);

R^9 is hydrogen; and

R^{10} is hydrogen.

[00122] In certain embodiments, the compound of Formula II is:

4-(4-Fluoro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Trifluoromethyl-phenyl)-piperazine-1-sulfonic acid amide;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

1-(4-Fluoro-3-trifluoromethyl-phenyl)-piperidine-4-carbonitrile;

4-(4-Methyl-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carbonitrile; or

4-(4-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile.

[00123] When considering compounds of Formula III, in certain embodiments, R^1 is hydrogen; and R^2 and R^3 are independently hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl; or R^2 and R^3, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring. In certain embodiments, R^1 and R^2, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; and R^3 is hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl.

[00124] In certain embodiments, R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl. In certain embodiments, R^2 is hydrogen, trifluoromethyl-, 4-methoxyphenyl-, 3-methylphenyl-, 2-fluorophenyl, or phenyl.

[00125] In certain embodiments, R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy. In certain embodiments, R^3 is trifluoromethyl, 2-chlorophenoxy, benzyl, 2-methylphenoxy-, 4-chlorophenoxy-, 3-chlorophenoxy-, phenoxy-, 4-fluorophenoxy, or 4-methylphenoxy-.

[00126] In certain embodiments, R^6 is hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is absent.

[00127] In certain embodiments, R^7 is hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl. In certain embodiments, R^7 is hydrogen.

[00128] In certain embodiments, R^8 is hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl. In certain embodiments, R^8 is cyano or optionally substituted aminosulfonyl. In certain embodiments, R^8 is cyano or aminosulfonyl.

[00129] In certain embodiments, R^9 is hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl. In certain embodiments, R^9 is hydrogen.

[00130] In certain embodiments, R^{10} is hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl. In certain embodiments, R^{10} is hydrogen.

[00131] In certain embodiments,

V' is N and W', X', Y', and Z' are C;

X is N;

R^1 is hydrogen;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

[00132] In certain embodiments,

V', W', X', Y', and Z' are C;

X is N;

R^1 is hydrogen;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

[00133] In certain embodiments,

V' is N and W', X', Y', and Z' are C;

X is CH;

R^1 is hydrogen;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

[00134] In certain embodiments,

V', W', X', Y', and Z' are C;

X is CH;

R^1 is hydrogen;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

[00135] In certain embodiments, the compound of Formula III is:

3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-Cyclohexyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(4-Trifluoromethyl-piperidin-1-yl)-benzenesulfonamide;

4-[3-(2-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;

4-Benzyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(3-o-Tolyloxy-piperidin-1-yl)-benzenesulfonamide;

6-(Octahydro-isoquinolin-2-yl)-nicotinonitrile;

3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-[3-(4-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;

4-[3-(3-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;

3-(3-Methyl-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-(2-Fluoro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(3-Phenoxy-piperidin-1-yl)-benzenesulfonamide;

6-(Octahydro-quinolin-1-yl)-nicotinonitrile;

3-Phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(4-p-Tolyloxy-piperidin-1-yl)-benzenesulfonamide; or

4-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-benzenesulfonamide.

[00136] When referring to compounds of Formula IV, in certain embodiments, A is phenyl, thiophen-3-yl, 1H-pyrrol-3-yl, furan-3-yl, oxazol-4-yl, thiazol-4-yl, or 1H-imidazol-4-yl, each of which is optionally substituted with one or two of the following groups: halogen, optionally substituted phenoxy, optionally substituted benzyl, optionally substituted aminophenyl, lower alkyl,

lower alkenyl, trifluoromethyl, difluoromethyl, difluoromethoxy, or trifluoromethoxy.

[00137] In certain embodiments, A is phenyl substituted at the 3-position with hydrogen, trifluoromethyl, difluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, propyl, isopropyl or t-butyl; and substituted at the 4-position with hydrogen, fluoro, chloro, phenoxy, 2-methylphenoxy-, 3-methylphenoxy-, 3-chlorophenoxy, 4-hydroxyphenoxy-, 2-chlorophenoxy-, 4-fluorophenoxy, 3-fluorophenoxy, 2-fluorophenoxy, 3-methoxyphenoxy-, 3-trifluoromethylphenoxy-, 2-fluoro-4-chlorophenoxy-, trifluoromethoxy, trifluoromethyl, propyl, methyl, or propenyl, provided that both substituents are not hydrogen.

[00138] In certain embodiments, A is thiophen-3-yl, or thiazol-4-yl, each of which is substituted with trifluoromethyl, difluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, propyl, isopropyl or t-butyl.

[00139] In certain embodiments, B is a 5- or 6-membered heteroaromatic ring which is substituted with one or two of the following groups: optionally substituted amino, acyl, cyano, sulfonyl, nitro, heterocycle, or optionally substituted aminocarbonyl, In certain embodiments, B is pyridinyl or pyrimidinyl, each of which is substituted with cyano, nitro, optionally substituted amino, or aminocarbonyl.

[00140] In certain embodiments,

A is phenyl substituted at the 3-position with trifluoromethyl, difluoromethyl, difluoromethoxy trifluoromethoxy, isopropyl, or t-butyl and substituted at the 4-position with hydrogen or fluoro; and

B is pyridinyl or pyrimidinyl, each of which is substituted with cyano, acylamino-, or aminocarbonyl.

TESTING

[00141] Test compounds can be assayed in a highly parallel fashion by using multiwell plates by placing the compounds either individually in wells or testing them in mixtures. Assay components including the target protein complex, coupling enzymes and substrates, and ATP can then be added to the

wells and the absorbance or fluorescence of each well of the plate can be measured with a plate reader.

[00142] In some embodiments, the method uses a 384 well plate format and a 25 μL reaction volume. A pyruvate kinase/lactate dehydrogenase coupled enzyme system (Huang TG and Hackney DD. (1994) **J Biol Chem 269**(23):16493-501, which is incorporated herein by reference) is used to measure the rate of ATP hydrolysis in each well. As will be appreciated by those in the art, the assay components are added in buffers and reagents. Since the methods outlined herein allow kinetic measurements, the incubation periods are optimized to give adequate detection signals over the background. The assay is done in real time giving the kinetics of ATP hydrolysis which increases the signal to noise ratio of the assay.

THERAPEUTIC UTILITIES

[00143] The compounds of Formulae I to III exhibit antifungal activity. For example, these compounds inhibit the growth of various infectious fungi including *Candida spp.* such as *Candida albicans*, *Candida tropicalis*, *Candida (Torulopsis) glabrata*, *Candida parapsilosis*, *Candida lusitaneae*, *Candida rugosa*, *Candida krusei*, and *Candida pseudotropicalis*, including certain fluconazole resistant fungal strains. In some embodiments, the compound is specific for *Candida albicans*. In some embodiments, the compound is specific for *Candida albicans*, including certain fluconazole resistant fungal strains. Fungal infections which can be inhibited or treated with the compounds and compositions provided herein include but are not limited to: candidiasis including but not limited to onychomycosis, chronic mucocutaneous candidiasis, oral candidiasis, epiglottitis, esophagitis, gastrointestinal infections, genitourinary infections, for example, caused by any *Candida* species, including those listed above.

[00144] A variety of cell-based assays may be used to determine activity. Among these are microtiter plate, disc plate diffusion, and inhibition of fungal hyphae length. These assays utilize standard techniques that are well-known in the art ((R.N. Jones et al, Manual of Clinical Microbiology, 4th ed., (1985); and M.A. Pfaller et al, Antimicrobial Agents and Chemotherapy, 34 (1990)).

[00145] Antifungal activity of a test compound can be determined *in vitro* by obtaining the minimum inhibitory concentration (MIC) of the compound using a standard agar dilution test or a disc-diffusion test. The compound is then tested *in vivo* (in mice) to determine the effective dose of the test compound for controlling a systemic fungal infection.

[00146] Accordingly, representative compounds of the present invention are tested for, and display, antifungal activity against at least one of the following fungi: *C. albicans, C. parapsilosis, C. neoformans, Histoplasma spp,* and *A. fumigatus*. Thus, in certain embodiments, the invention herein includes application to cells or individuals afflicted or impending affliction with any one of these disorders or states.

FORMULATION AND ADMINISTRATION

[00147] The compounds, pharmaceutically acceptable salts and solvates of Formula I, II, III, or IV are administered at a therapeutically effective dosage, e.g., a dosage sufficient to provide treatment for the disease states previously described. Human dosage levels are typically determined by escalating dose ranging studies conducted in accordance with current Good Clinical Practice, FDA and local guidelines. The amount of active compound administered will, of course, be dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician.

[00148] The administration of the compounds and pharmaceutical formulations of the present invention can be done in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In some instances, the compound or composition may be directly applied as a solution or spray.

[00149] Pharmaceutical formulations include a compound of Formula 1, 2, 3 or 4 or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. As is known in the art, pharmaceutical excipients are secondary ingredients that function to enable or enhance the delivery of a drug or medicine in a variety of dosage forms (e.g.: oral forms such

as tablets, capsules, and liquids; topical forms such as dermal, opthalmic, and otic forms; suppositories; injectables; respiratory forms and the like). Pharmaceutical excipients include inert or inactive ingredients, synergists or chemicals that substantively contribute to the medicinal effects of the active ingredient. For example, pharmaceutical excipients may function to improve flow characteristics, product uniformity, stability, taste, or appearance, to ease handling and administration of dose, for convenience of use, or to control bioavailability. While pharmaceutical excipients are commonly described as being inert or inactive, it is appreciated in the art that there is a relationship between the properties of the pharmaceutical excipients and the dosage forms containing them.

[00150] Pharmaceutical excipients suitable for use as carriers or diluents are well known in the art, and may be used in a variety of formulations. See, e.g., Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, Editor, Mack Publishing Company (1990); Remington: The Science and Practice of Pharmacy, 20th Edition, A. R. Gennaro, Editor, Lippincott Williams & Wilkins (2000); Handbook of Pharmaceutical Excipients, 3rd Edition, A. H. Kibbe, Editor, American Pharmaceutical Association, and Pharmaceutical Press (2000); and Handbook of Pharmaceutical Additives, compiled by Michael and Irene Ash, Gower (1995). The concentration of a therapeutically active agent in a formulation can vary widely, from about 0.1 to 99.9 wt.%, depending on the nature of the formulation.

[00151] Oral solid dosage forms such as tablets will typically comprise one or more pharmaceutical excipients, which may for example help impart satisfactory processing and compression characteristics, or provide additional desirable physical characteristics to the tablet. Such pharmaceutical excipients may be selected from diluents, binders, glidants, lubricants, disintegrants, colorants, flavorants, sweetening agents, polymers, waxes or other solubility-modulating materials.

[00152] Dosage forms for parenteral administration will generally comprise fluids, particularly intravenous fluids, i.e., sterile solutions of simple chemicals such as sugars, amino acids or electrolytes, which can be easily carried by the circulatory system and assimilated. Such fluids are typically prepared with water

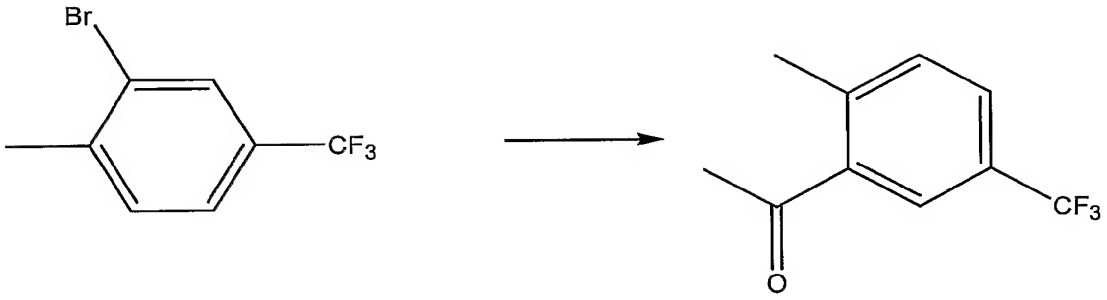
for injection USP. Fluids used commonly for intravenous (IV) use are disclosed in Remington, The Science and Practice of Pharmacy [full citation previously provided]. The pH of such IV fluids may vary, and will typically be from 3.5 to 8 as known in the art.

[00153] Formulations of the active compound or a salt may also be administered to the respiratory tract as an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation have diameters of less than 50 microns, in some embodiments, less than 10 microns.

[00154] The following examples serve to more fully describe the manner of practicing the above-described invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes.

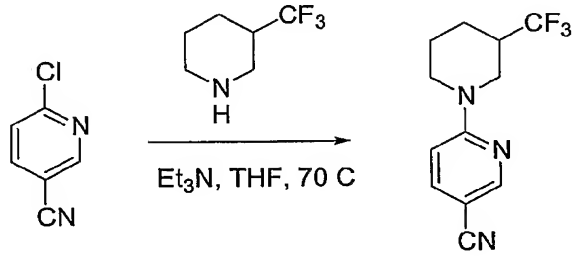
EXAMPLES

EXAMPLE 1



[00155] A mixture of 2-bromo-4-trifluoromethyl toluene (1 equivalent), n-butyl vinyl ether (5 equivalents), palladium acetate (0.1 equivalents), DPPP (0.22 equivalents), K_2CO_3 (1.2 equivalents), and DMF-H_2O (0.3 M to bromide) was stirred under N_2 for 18 hours at 100°C. The reaction mixture was then cooled to room temperature and hydrolyzed with 5% HCl for 30 min. Extraction with EtOAc, washing with H_20, sat aq. NaCl, drying ($MgSO_4$), and concentration gave an oil. Purification of the crude material by silica gel flash chromatography using an 0% hexanes to 50% hexanes-EtOAc gradient gave 2'-methyl-5'-trifluoromethylacetophenone: the compound prepared showed a molecular ion M- = 201.1.

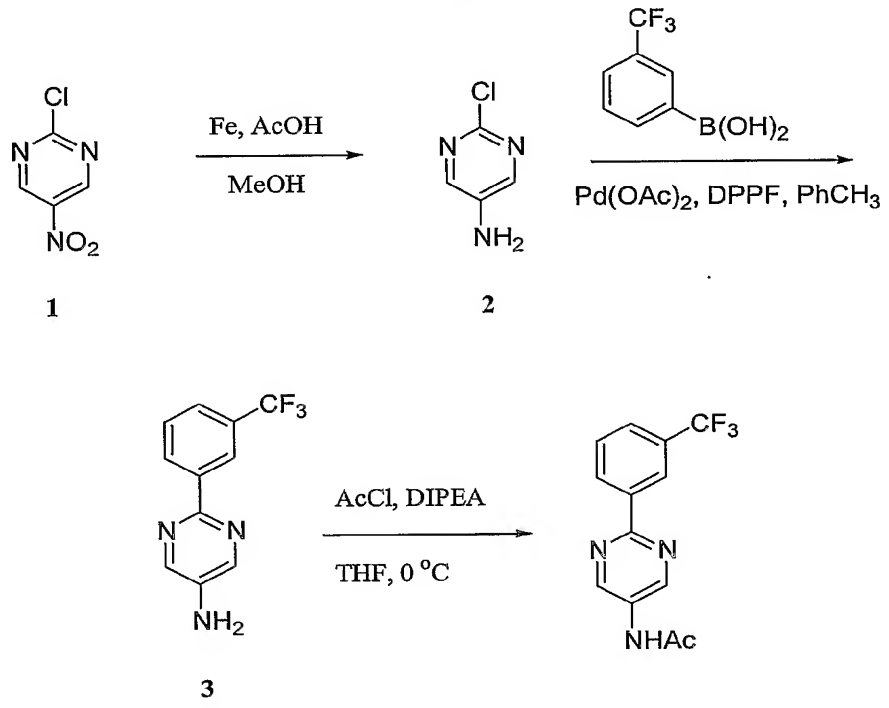
EXAMPLE 2



[00156] A solution of 2-chloro-5-nitropyridine (2.1g, 15.3 mmol), dl-3-trifluormethyl-piperidine (3.29 g, 21.4 mmol), triethyl amine (6.6 mL, 46 mmol), and THF (50 mL) was heated at 70 C for 16 h. The volatiles were then removed

in-vacuo and the residue partitioned between EtOAc (100 mL) and H2O (100 mL). The organic layer was separated, washed with saturated aqueous NH4Cl (50 mL) and saturated aqueous NaCl (75 mL), dried (Mg SO4), and concentrated *in-vacuo* to give a viscous oil. Chromatography of this material on silica gel using a Hexanes/EtOAc gradient (0% EtOAc to 50% EtOAc) gave 3-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile as a colorless solid (3.0 g, 11.7 mmol, 77% yield, m/z + = 256.1).

EXAMPLE 3



1 2 3

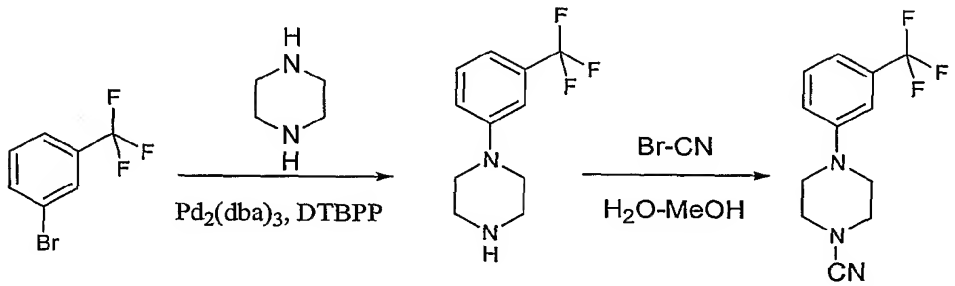
[00157] **5-Amino-2-chloro-pyrimidine (2).** Acetic acid (15 mL, 261 mmol, 8 equiv) was slowly added to a stirred mixture of iron powder (11 g, 196 mmol, 6 equiv), 2-chloro-5-nitro-pyrimidine (5.3 g, 33.33 mmol, 1 equiv), and methanol (75 mL). Note: the reaction will exotherm if the acetic acid is added rapidly. After three hours, the reaction mixture was diluted with EtOAc (300 mL), filtered through celite, and neutralized with aqueous K_2CO_3 (200 mL). The organic layer was separated, washed with H_2O (200 mL) and brine (200 mL), dried

(Na_2SO_4), filtered, and concentrated to give **2** as a yellow solid (2.5 g, 58%, m/z+ = 130.1).

[00158] **4-Amino-2-(3-triflouromethylphenyl)-pyrimidine (3).** A mixture of 5-Amino-2-chloro-pyrimidine (4.5 g, 34.9 mmol), 3-trifuoromethylphenylboronic acid (9.9 g, 52.3 mmol), Pd(OAc)2 (390 mg, 1.74 mmol), DPPF (963 mg, 1.74 mmol), 2 M aqueous K2CO3 (52 mL), and toluene (100 mL) were heated at 110 C for 16 h. The mixture was diluted with EtOAc (100 mL) and the organic layer washed with H2O (100 mL) and brine (100 mL). Drying (MgSO4) and removal of the volatiles *in-vacuo* gave a dark brown solid. Chromatography of this material on silica gel using a Hexanes/EtOAc gradient (20% EtOAc to 80% EtOAc) gave **3** as a colorless solid (3.5 g, 14.6 mmol, 41% yield, m/z + = 240.1).

[00159] Acetyl chloride (40 mg,0.50 mmol) was slowly added to a 0 C solution of amino-2-(3-triflouromethylphenyl)-pyrimidine (100 mg, 0.41 mmol), pyridine (200 uL), and THF (2 mL). After 8 h, the solution was concentrated *in-vacuo* to give a yellow residue. Chromatography of this material on silica gel using a Hexanes/EtOAc gradient (10% EtOAc to 80% EtOAc) gave N-[2-(3-trifluoromethyl-phenyl)-pyrimidin-5-yl]-acetamide as a colorless solid (97 mg, 0.34 mmol, 85% yield, m/z - = 280.1).

EXAMPLE 4



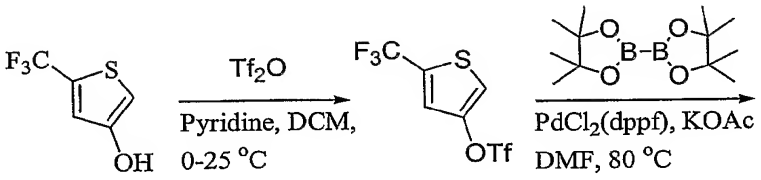
1

[00160] **1-N-(3-trifuoromethylphenyl)piperidine (1)** A mixture of piperidine (3.54g, 41.0 mmol), 3-bromobenzotrifluoride (4.60 g, 20.6 mmol),

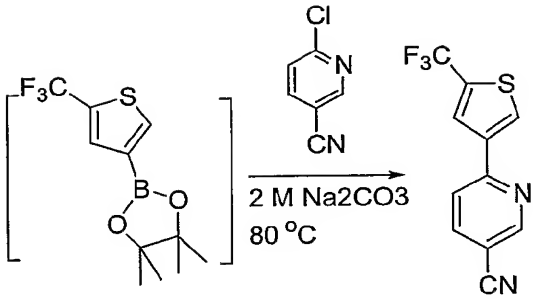
potassium phosphate (6.10 g, 28.8 mmol), 2-di-*tert*-butylphosphinobiphenyl (0.835g, 2.80 mmol), tris(dibenzylideneacetone)dipalladium (1.28g, 1.4 mmol), and toluene (42 mL) were stirred for 16 h. The mixture was then filtered through celite and the filtrate washed with water (2 x 50 mL) and brine (1 x 50 mL), dried (NaSO4), and concentrated to a solid. Chromatography of this material on silica gel using Hexanes/Ethyl Acetate (2:3) yielded **1** (3.63 g, 15.8 mmol, 77%, m/z + = 231).

[00161] **4'N-cyano, 1-N-(3-trifuoromethylphenyl)piperidine** A solution of 1-N-(3-trifuoromethylphenyl)piperidine (3.63 g, 15.8mmol), cyanogen bromide (16.8 g, 158 mmol), methanol (75 mL), and H20 (75 mL) was maintained at room temperature for 4 h. The solution was stirred for 4 h and then the volatiles were removed *in-vacuo* to give a solid. The crude solid was dissolved in EtOAc (100 mL) and this organic solution was washed with 1 N NaOH (3 x 100 mL), 1 M HCl (3 x 100 mL), brine (1 x 100 mL), dried (Na2SO4), and then concentrated to give 4-(3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile as a solid (3.78 g, 14.8 mmol, 94%, m/z + = 256).

EXAMPLE 5



1



2

[00162] **4-Trifluoromethanesulfonate-2-trifluoromethylthiophene (1)** . Trifluoromethanesulfonic anhydride (12 ml, 92.8 mmol, 2 eq.) was added drop-wise to a 0 C solution of 3-hydroxy-5-trifluoromethylthiophene (7.8 g, 46.4 mmol, prepared as in Synthesis 2000 get reference), pyridine (7.4 ml, 92.8 mmol, 2 eq.), and dichloromethane (230 ml). The mixture was allowed to warm to rt and maintained for 3 h. At this time, the solution was diluted with dichloromethane (200 ml), washed with brine (100 ml), 1 M HCl (100 ml), and brine (100 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated to yield **1** as a reddish-orange oil (12.8 g, 92 %).

[00163] A solution of 4-trifluoromethanesulfonate-2-trifluoromethylthiophene (2 g, 6.7 mmol), bis(pinacolato)diboron (3.4 g, 13.3 mmol,), KOAc (3.3 g, 33.5 mmol,), $PdCl_2$(dppf) (1.5 g, 2.0 mmol,) in DMF (67 mL) was stirred at 80 °C for 1 h. At this time, 2-chloronicotinonitrile (1.1 g, 7.2 mmol) was added followed by a solution of 2 M sodium carbonate (10 ml, 20.1 mmol). The resulting mixture was heated at 80 C for an additional 16 h. Then, the reaction mixture was cooled to room temperature and diluted with EtOAc (300 mL). The organic layer was washed with brine (50 ml x 3), dried ($MgSO_4$), and concentrated to a brown oil. Chromatography of this material on silica gel using Hexanes/Ethyl Acetate (10:1) yielded a colorless solid (850 mg). The solid was further purified by reverse phase HPLC to obtain 6-(5-trifluoromethyl-thiophen-3-yl)-nicotinonitrile as colorless solid (800 mg, 50 %, m/z + = 255.3).

EXAMPLE 6

[00164] This example illustrates the preparation of a representative pharmaceutical formulation for topical application containing an active compound of Formula I, II, III, or IV.

Ingredients		grams
Active compound		0.2-10
Span 60		2
Tween 60		2
Mineral oil		5
Petrolatum		10
Methyl paraben		0.15
Propyl paraben		0.05
BHA (butylated hydroxy anisole)		0.01
Water	q.s. to	100

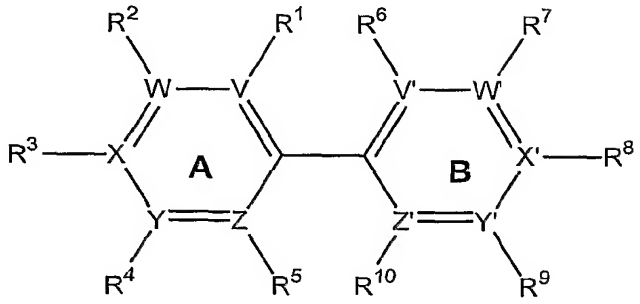
The above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

[00165] Other compounds of Formula I, II, III, or IV, such as those prepared in accordance with Examples 1-5, can be used as the active compound in the preparation of the topical formulations of this example.

[00166] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. All patents and publications cited above are hereby incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

What is claimed is:

1. A compound represented by Formula I:



Formula I

wherein:

R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, or sulfanyl,

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, substituted alkyl, optionally substituted alkoxy, acyl, optionally substituted amino, alkoxycarbonyl, cyano, nitro, sulfinyl, or sulfonyl;

W, X, Y, Z, W', X', Y' and Z' are independently N, C, O, or S; and

V and V' are independently N, C, O, S or absent

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, provided that:

at least one of R^1, R^2, R^3, R^4 and R^5 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

at least one of V, W, X, Y, Z, V', W', X', Y' and Z' is N, O or S;

no more than two of V, W, X, Y and Z are N;

no more than two of V', W', X', Y' or Z' are N;

W, X, Y or Z is O or S only when V is absent;

W', X', Y' or Z' is O or S only when V' is absent;

R^1, R^2, R^3, R^4 or R^5 is absent when V, W, X, Y or Z, respectively, is N, O, S or absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent.

2. The compound of Claim 1 comprising one or more of the following:

V is absent, X is S, and W, Y, and Z are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

3. The compound of Claim 2 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-; and

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino-.

4. The compound of Claim 3 wherein

R^2 is hydrogen and R^4 is trifluoromethyl, trifluoromethoxy, propenyl, styrenyl, 1-methylbenzyl-, 4-chlorobenzyl, 4-chlorobenzyl, 2-chloro-4-fluorobenzyl, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-methoxybenzyl, bromo, cyclopropyl, t-butyl, or isopropyl.

5. The compound of any of Claims 1 to 4 wherein R^8 is cyano or cyanoamino-.

6. The compound of Claim 5 wherein R^7 and R^9 are hydrogen.

7. The compound of Claim 1 comprising one or more of the following:

V is absent, X is S, Z is N, and W and Y are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is absent;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

8. The compound of Claim 7 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-; and

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino-.

9. The compound of Claim 8 wherein

R^2 is hydrogen and R^4 is trifluoromethyl, trifluoromethoxy, propenyl, styrenyl, 1-methylbenzyl-, 4-chlorobenzyl, 4-chlorobenzyl, 2-chloro-4-fluorobenzyl, benzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-fluorobenzyl, 3-methoxybenzyl, bromo, cyclopropyl, t-butyl, or isopropyl.

10. The compound of any of Claims 7 to 9 wherein R^8 is cyano or cyanoamino-.

11. The compound of Claim 1 comprising one or more of the following:

V, W, X, Y, and Z are C;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is hydrogen, halogen, optionally substituted phenoxy, lower alkyl, lower alkenyl, trifluoromethyl, or trifluoromethoxy;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted

aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

12. The compound of Claim 11 comprising one or more of the following:

R^1 is fluoro;

R^2 is hydrogen, trifluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, or propyl;

R^3 is fluoro, chloro, phenoxy, 2-methylphenoxy-, 3-methylphenoxy-, 3-chlorophenoxy, 4-hydroxyphenoxy-, 2-chlorophenoxy-, 4-fluorophenoxy, 3-fluorophenoxy, 2-fluorophenoxy, 3-methoxyphenoxy-, 3-trifluoromethylphenoxy-, 2-fluoro-4-chlorophenoxy-, trifluoromethoxy, trifluoromethyl, propyl, methyl, or propenyl;

R^4 is isopropyl, propenyl, trifluoromethyl, trifluoromethoxy, styrenyl-, bromo, optionally substituted benzyl, cyclopropyl, or t-butyl;

R^5 is hydrogen;

V' is N and R^6 is absent;

R^7 is amino, aminosulfonyl-, 2-hydroxyethoxy-, cyanomethyl-, or 2-methoxyethoxy-; and

R^8 is hydrogen, amino, formylamino-, acetylamino-, cyano, aminosulfonylamino-, aminosulfonyl, cyanoamino-, carbamoyl, methylcarbamoyl, ixoxazolylcarbonylamino-, carbmoyl-amino-, or methylcarbamoyl-amino-.

13. The compound of Claim 12 wherein one of R^2 or R^3 is trifluoromethyl, trifluoromethoxy, or isopropyl; and the other is hydrogen or fluoro.

14. The compound of any of Claims 11 to 13 wherein R^8 is cyano or cyanoamino-.

15. The compound of Claim 1 wherein

V is absent, X is S, and W, Y, and Z are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

16. The compound of Claim 1 wherein

V is absent, X is S, Z is N, and W and Y are C;

R^1 is absent;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is absent;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is absent;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

17. The compound of Claim 1 wherein

V, W, X, Y, and Z are C;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, optionally substituted lower alkyl; cyclohexyl, lower alkenyl, optionally substituted lower alkoxyl, phenyl, or methylsulfanyl;

R^3 is hydrogen, halogen, optionally substituted phenoxy, lower alkyl, lower alkenyl, trifluoromethyl, or trifluoromethoxy;

R^4 is hydrogen, halogen, optionally substituted methyl, optionally substituted methoxy, styrenyl, cyclopropyl, or optionally substituted propenyl;

R^5 is hydrogen;

V' is N and R^6 is absent, or V' is C and R^6 is hydrogen;

W', X', Y' and Z' are C;

R^7 is hydrogen, optionally substituted amino, optionally substituted lower alkoxyl, optionally substituted methyl, cyano, nitro, or optionally substituted aminosulfonyl,

R^8 is hydrogen, optionally substituted amino, cyano, sulfonyl, nitro, or optionally substituted aminocarbonyl,

R^9 is hydrogen; and

R^{10} is hydrogen.

18. The compound of Claim 1 wherein ring B is nicotinonitrile-6-yl and ring A is:

4-fluoro-3-trifluoromethyl-phenyl,
2-methylphenoxy,
3-chloro-4-trifluoromethoxy-phenyl,
5-benzyl-thiazol-3-yl,
5-benzyl-thien-2-yl,
biphen-3-yl
2-bromothien-4-yl,
5-(4-chlorobenzyl)-thien-2-yl,

4-chloro-5-isopropenylphenyl,
5-(4-chlorobenzyl)-thiazol-2-yl,
5-(2-chloro-4-fluorobenzyl)-thiazol-2-yl,
4-chloro-5-methylphenyl,
2-chlorophenoxyphenyl,
3-chlorophenoxyphenyl,
3-chlorophenyl,
4-chloro-5-fluorophenyl,
4-chloro-3-trifluoromethylphenyl,
4-cyano-5-trifluoromethylphenyl,
3-cyclohexylphenyl,
3-cyclopropylphenyl,
5-cyclopropyl-thiazol-2-yl,
2-(2,4-dichlorobenzyl)-thiazol-4-yl,
3-difluoromethoxyphenyl,
3-(1,1-difluoropropyl)phenyl,
3-ethylphenyl,
2-(2-fluorobenzyl)-thiazol-4-yl,
2-(3-fluorobenzyl)-thiazol-4-yl,
2-(4-fluorobenzyl)-thiazol-4-yl,
4-(3-fluorophenoxy)-phenyl,
4-(4-fluorophenoxy)-phenyl,
4-fluoro-3-isopropenylphenyl,
2-fluorophenoxyphenyl,
2-fluoro-3-trifluoromethylphenyl,
2-fluoro-3-trifluoromethylphenyl,
3-fluoro-4-trifluoromethylphenyl,
4-(4-hydroxyphenoxy)-phenyl,
5-isopropenyl-thiazol-2-yl,
5-isopropyl-thiazol-2-yl,
3-isopropyl-phenyl,
2-isopropenyl-thien-4-yl,
2-isopropyl-thien-4-yl,

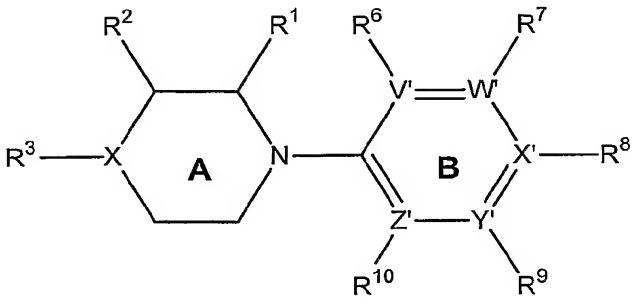
2-isopropyl-thien-5-yl,
3-isopropyl-4-fluorophenyl,
5-(1-Phenyl-ethyl)-thiophen-3-yl,
2-(4-Chloro-2-fluoro-benzyl)-thiazol-4-yl,
2-tert-Butyl-thiazol-4-yl,
5-tert-Butyl-thiophen-3-yl,
5-Isopropyl-thiophen-3-yl,
2-(3-methoxybenzyl)-thiazol-4-yl,
2-(4-methoxybenzyl)-thiazol-4-yl,
4-(3-methoxyphenoxy)-phenyl,
2-(3-methylbenzyl)-thiazol-4-yl,
5-(4-methylbenzyl)-thiazol-2-yl,
4-(2-methylphenoxy)phenyl,
methyl-phenyl-thiazol-2-yl-amine,
2-(1-methyl-2-phenethyl)-thien-4-yl,
2-(1-methyl-2-phenylvinyl)-thien-4-yl,
3-methylsulfanylphenyl,
4-methyl-5-trifluoromethylphenyl,
4-phenoxyphenyl,
2-(1-phenylvinyl)-thien-4-yl,
2-trifluoromethoxyphenyl,
3-trifluoromethoxyphenyl,
4-trifluoromethoxyphenyl,
4-(3-trifluoromethylphenoxy)-phenyl,
2-trifluoromethyl-benzoic acid methyl ester,
2-trifluoromethyl-thien-4-yl,
3-trifluoromethylphenyl,
3-(2,2,2-trifluoroethyl)phenyl,
2-[1-(4-Chloro-phenyl)-1-methyl-ethyl]-thiazol-4-yl, or
5-trifluoromethyl-thiazol-2-yl.

19. The compound of Claim 1 wherein ring B is pyrimidine-5-carbonitrile and ring A is:

5-benzyl-thiazol-3-yl,
5-tert-Butyl-thiophen-3-yl,
5-benzyl-thien-2-yl,
biphen-3-yl,
2-bromothien-4-yl,
5-(4-chlorobenzyl)-thien-2-yl,
4-chloro-5-isopropenylphenyl,
5-(4-chlorobenzyl)-thiazol-2-yl,
5-(2-chloro-4-fluorobenzyl)-thiazol-2-yl,
4-chloro-5-methylphenyl,
2-chlorophenoxyphenyl,
3-chlorophenoxyphenyl,
3-chlorophenyl,
4-chloro-5-fluorophenyl,
4-chloro-5-trifluoromethylphenyl,
4-cyano-5-trifluoromethylphenyl,
3-cyclohexylphenyl,
3-cyclopropylphenyl,
5-cyclopropyl-thiazol-2-yl,
2-(2,4-dichlorobenzyl)-thiazol-4-yl,
3-difluoromethoxyphenyl,
3-(1,1-difluoropropyl)phenyl,
3-ethylphenyl,
2-(2-fluorobenzyl)-thiazol-4-yl,
2-(3-fluorobenzyl)-thiazol-4-yl,
2-(4-fluorobenzyl)-thiazol-4-yl,
4-(3-fluorophenoxy)-phenyl,
4-(4-fluorophenoxy)-phenyl,
4-fluoro-5-isopropenylphenyl,
2-fluorophenoxyphenyl,
2-fluoro-3-trifluoromethylphenyl,
2-fluoro-3-trifluoromethylphenyl,
3-fluoro-4-trifluoromethylphenyl,

4-(4-hydroxyphenoxy)-phenyl,
5-isopropenyl-thiazol-2-yl,
5-isopropyl-thiazol-2-yl,
2-isopropenyl-thien-4-yl,
2-isopropyl-thien-4-yl,
2-(3-methoxybenzyl)-thiazol-4-yl,
2-(4-methoxybenzyl)-thiazol-4-yl,
4-(3-methoxyphenoxy)-phenyl,
2-(3-methylbenzyl)-thiazol-4-yl,
5-(4-methylbenzyl)-thiazol-2-yl,
4-(2-methylphenoxy)phenyl,
methyl-phenyl-thiazol-2-yl-amine,
2-(1-methyl-2-phenethyl)-thien-4-yl,
2-(1-methyl-2-phenylvinyl)-thien-4-yl,
3-methylsulfanylphenyl,
4-methyl-5-trifluoromethylphenyl,
4-phenoxyphenyl,
2-(1-phenylvinyl)-thien-4-yl,
2-trifluoromethoxyphenyl,
4-trifluoromethoxyphenyl,
4-(3-trifluoromethylphenoxy)-phenyl,
2-trifluoromethyl-benzoic acid methyl ester,
2-trifluoromethyl-thien-4-yl,
3-trifluoromethylphenyl,
2-(2,2,2-trifluoroethyl)phenyl,
5-tert-Butyl-thiophen-3-yl, or
5-trifluoromethyl-thiazol-2-yl.

20. A compound represented by Formula II:



Formula II

wherein:

X is CH or N;

R^1 and R^2 are independently hydrogen, halogen, hydroxyl, or lower alkyl;

R^3 is cyano or sulfonyl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, lower alkoxy, alkoxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, cyano, sulfanyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy;

V' is N, C, O, S or absent;

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

21. The compound of Claim 20 comprising one or more of the following:

V' is N and W', X' Y', and Z" are C;

X is N;

R^1 and R^2 are hydrogen,
R^3 is cyano or sulfonyl;
R^6 is absent;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

22. The compound of Claim 21 comprising one or more of the following:
R^7 is trifluoromethyl, and
R^8 is fluoro, chloro, methyl, or trifluoromethyl.

23. The compound of Claim 20 comprising one or more of the following
V', W', X' Y', and Z' are C;
X is N;
R^1 and R^2 are hydrogen;
R^3 is cyano or sulfonyl;
R^6 is hydrogen;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

24. The compound of Claim 23 comprising one or more of the following
R^6 is hydrogen;
R^7 is trifluoromethyl, and
R^8 is fluoro, chloro, methyl, or trifluoromethyl.

25. The compound of Claim 20 comprising one or more of the following:
V' is N and W', X' Y', and Z' are C;
X is C;
R^1 and R^2 are hydrogen,
R^3 is cyano or sulfonyl;

R^6 is absent;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

26. The compound of Claim 25 comprising one or more of the following:
R^7 is trifluoromethyl, and
R^8 is fluoro, chloro, methyl, or trifluoromethyl.

27. The compound of Claim 20 comprising one or more of the following
V', W', X' Y', and Z' are C;
X is C;
R^1 and R^2 are hydrogen;
R^3 is cyano or sulfonyl;
R^6 is hydrogen;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

28. The compound of Claim 27 comprising one or more of the following
R^6 is hydrogen;
R^7 is trifluoromethyl, and
R^8 is fluoro, chloro, methyl, or trifluoromethyl.

29. The compound of Claim 20 wherein:
V' is N and W', X' Y', and Z' are C;
X is N;
R^1 and R^2 are hydrogen,
R^3 is cyano or sulfonyl;
R^6 is absent;
R^7 is hydrogen or optionally substituted lower alkyl;

R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

30. The compound of Claim 20 wherein:
V', W', X' Y', and Z' are C;
X is N;
R^1 and R^2 are hydrogen;
R^3 is cyano or sulfonyl;
R^6 is hydrogen;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

31. The compound of Claim 20 wherein:
V' is N and W', X' Y', and Z' are C;
X is C;
R^1 and R^2 are hydrogen,
R^3 is cyano or sulfonyl;
R^6 is absent;
R^7 is hydrogen or optionally substituted lower alkyl;
R^8 is hydrogen, halogen, optionally substituted lower alkyl;
R^9 is hydrogen; and
R^{10} is hydrogen.

32. The compound of Claim 20 wherein:
V', W', X' Y', and Z' are C;
X is C;
R^1 and R^2 are hydrogen;
R^3 is cyano or sulfonyl;
R^6 is hydrogen;
R^7 is hydrogen or optionally substituted lower alkyl;

R^8 is hydrogen, halogen, optionally substituted lower alkyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

33. The compound of Claim 20 that is:

4-(4-Fluoro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

4-(4-Trifluoromethyl-phenyl)-piperazine-1-sulfonic acid amide;

4-(3-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

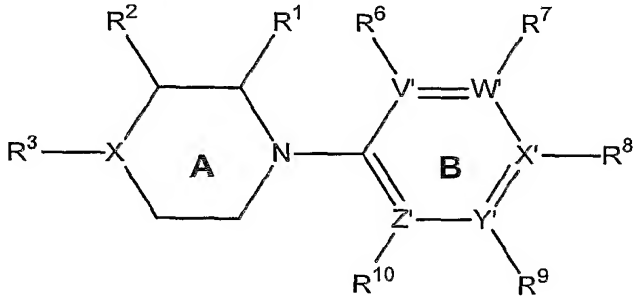
1-(4-Fluoro-3-trifluoromethyl-phenyl)-piperidine-4-carbonitrile;

4-(4-Methyl-3-trifluoromethyl-phenyl)-piperazine-1-carbonitrile;

1-(3-Trifluoromethyl-phenyl)-piperidine-4-carbonitrile; or

4-(4-Trifluoromethyl-phenyl)-piperazine-1-carbonitrile.

34. A compound represented by Formula III:



Formula III

wherein:

X is CH, O or N;

R^1 is hydrogen; and R^2 and R^3 are independently hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl; or R^2 and R^3, taken together with the atoms to which they are bound, form an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; or

R^1 and R^2, taken together with the atoms to which they are bound, form

an optionally substituted 5- to 7-membered ring, which optionally may include one additional heteroatoms selected from N, O, and S in the ring; and R^3 is hydrogen, optionally substituted alkyl, optionally substituted aryloxy, or optionally substituted aryl;

R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, hydroxy, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, cyano, or sulfonyl;

V' is N, C, O, S or absent,

and

W', X', Y' and Z' are independently N, C, O, or S,

provided that:

at least one of R^1, R^2 and R^3 is not hydrogen;

at least one of R^6, R^7, R^8, R^9 and R^{10} is not hydrogen;

no more than two of V', W', X', Y' or Z' are N;

W', X', Y' or Z' is O or S only when V' is absent; and

R^6, R^7, R^8, R^9 or R^{10} is absent when V', W', X,' Y' or Z', respectively, is N, O, S or absent,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

35. The compound of Claim 34 comprising one or more of the following:

V' is N and W', X', Y', and Z' are C;

X is N;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

36. The compound of Claim 35 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl-, 4-methoxyphenyl-, 3-methylphenyl-, 2-fluorophenyl, or phenyl;

R^3 is trifluoromethyl, 2-chlorophenoxy, benzyl, 2-methylphenoxy-, 4-chlorophenoxy-, 3-chlorophenoxy-, phenoxy-, 4-fluorophenoxy, or 4-methylphenoxy-;

R^7 is hydrogen; and

R^8 is cyano or aminosulfonyl.

37. The compound of Claim 34 comprising one or more of the following:

V', W', X', Y', and Z' are C;

X is N;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

38. The compound of Claim 34 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl-, 4-methoxyphenyl-, 3-methylphenyl-, 2-fluorophenyl, or phenyl;

R^3 is trifluoromethyl, 2-chlorophenoxy, benzyl, 2-methylphenoxy-, 4-chlorophenoxy-, 3-chlorophenoxy-, phenoxy-, 4-fluorophenoxy, or 4-methylphenoxy-; and

R^8 is cyano or aminosulfonyl.

39. The compound of Claim 34 comprising one or more of the following:

V' is N and W', X', Y', and Z' are C;

X is CH;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

40. The compound of Claim 39 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl-, 4-methoxyphenyl-, 3-methylphenyl-, 2-fluorophenyl, or phenyl;

R^3 is trifluoromethyl, 2-chlorophenoxy, benzyl, 2-methylphenoxy-, 4-chlorophenoxy-, 3-chlorophenoxy-, phenoxy-, 4-fluorophenoxy, or 4-methylphenoxy-; and

R^8 is cyano or aminosulfonyl.

41. The compound of Claim 34 comprising one or more of the following:

V', W', X', Y', and Z ' are C;

X is CH;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

42. The compound of Claim 41 comprising one or more of the following:

R^2 is hydrogen, trifluoromethyl-, 4-methoxyphenyl-, 3-methylphenyl-, 2-

fluorophenyl, or phenyl;

R^3 is trifluoromethyl, 2-chlorophenoxy, benzyl, 2-methylphenoxy-, 4-chlorophenoxy-, 3-chlorophenoxy-, phenoxy-, 4-fluorophenoxy, or 4-methylphenoxy-; and

R^8 is cyano or aminosulfonyl.

43. The compound of Claim 34 wherein:

V' is N and W', X', Y', and Z' are C;

X is N;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

44. The compound of Claim 34 wherein:

V', W', X', Y', and Z' are C;

X is N;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

45. The compound of Claim 34 wherein:

V' is N and W', X', Y', and Z' are C;

X is CH;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is absent;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

46. The compound of Claim 34 wherein:

V', W', X', Y', and Z' are C;

X is CH;

R^2 is hydrogen, optionally substituted lower alkyl, cyclohexyl, or optionally substituted phenyl;

R^3 is hydrogen, optionally substituted methyl, or optionally substituted phenoxy;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is cyano or optionally substituted aminosulfonyl;

R^9 is hydrogen; and

R^{10} is hydrogen.

47. The compound of Claim 34 that is

3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-Cyclohexyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

3-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(4-Trifluoromethyl-piperidin-1-yl)-benzenesulfonamide;

4-[3-(2-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;

4-Benzyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;

4-(3-o-Tolyloxy-piperidin-1-yl)-benzenesulfonamide;

6-(Octahydro-isoquinolin-2-yl)-nicotinonitrile;
3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;
4-[3-(4-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;
4-[3-(3-Chloro-phenoxy)-piperidin-1-yl]-benzenesulfonamide;
3-(3-Methyl-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;
3-(2-Fluoro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;
4-(3-Phenoxy-piperidin-1-yl)-benzenesulfonamide;
6-(Octahydro-quinolin-1-yl)-nicotinonitrile;
3-Phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;
3-(4-Methoxy-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carbonitrile;
4-(4-p-Tolyloxy-piperidin-1-yl)-benzenesulfonamide; or
4-[4-(4-Fluoro-phenoxy)-piperidin-1-yl]-benzenesulfonamide.

48. A compound represented by Formula IV:

A-B

Formula IV

wherein

A is phenyl, thiophen-3-yl, 1H-pyrrol-3-yl, furan-3-yl, oxazol-4-yl, thiazol-4-yl, or 1H-imidazol-4-yl, each of which is optionally substituted with one or two of the following groups: halogen, optionally substituted phenoxy, optionally substituted benzyl, optionally substituted aminophenyl, lower alkyl, lower alkenyl, trifluoromethyl, difluoromethyl, difluoromethoxy, or trifluoromethoxy; and

B is a 5- or 6-membered heteroaromatic ring which is substituted with one or two of the following groups: optionally substituted amino, acyl, cyano, sulfonyl, nitro, heterocycle, or optionally substituted aminocarbonyl,

or a single stereoisomer, mixture of stereoisomers, or a pharmaceutically acceptable salt thereof

49. The compound of claim 48 wherein

A is phenyl substituted at the 3-position with hydrogen, trifluoromethyl, difluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy,

difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, propyl, isopropyl or t-butyl; and substituted at the 4-position with hydrogen, fluoro, chloro, phenoxy, 2-methylphenoxy-, 3-methylphenoxy-, 3-chlorophenoxy, 4-hydroxyphenoxy-, 2-chlorophenoxy-, 4-fluorophenoxy, 3-fluorophenoxy, 2-fluorophenoxy, 3-methoxyphenoxy-, 3-trifluoromethylphenoxy-, 2-fluoro-4-chlorophenoxy-, trifluoromethoxy, trifluoromethyl, propyl, methyl, or propenyl, provided that both substituents are not hydrogen; or

A is thiophen-3-yl, or thiazol-4-yl, each of which is substituted with trifluoromethyl, difluoromethyl, fluoro, chloro, trifluoroethyl-, propenyl, trifluoromethoxy, difluoromethoxy, 1,1-difluoropropyl-, ethyl, methyl, propyl, isopropyl or t-butyl.

50. The compound of claim 48 or 49 wherein B is pyridinyl or pyrimidinyl, each of which is substituted with cyano, nitro, optionally substituted amino, or aminocarbonyl.

51. The compound of any of claims 48 to 50 wherein

A is phenyl substituted at the 3-position with trifluoromethyl, difluoromethyl, difluoromethoxy, trifluoromethoxy, isopropyl, or t-butyl and substituted at the 4-position with hydrogen or fluoro; and

B is pyridinyl or pyrimidinyl, each of which is substituted with cyano, acylamino-, or aminocarbonyl.

52. A method for treating a fungal infection comprising administering to a mammal suffering from such an infection a therapeutically effective amount of a compound of any of Claims 1-51.

53. The method of Claim 52 wherein said compound inhibits C. albicans Kip1.

54. A pharmaceutical formulation comprising a compound of any of Claims 1-51 and a pharmaceutically acceptable excipient.